CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-287/S-035

Trade Name: FRAGMIN

Generic Name: Dalteparin sodium injection

Sponsor: Pharmacia & Upjohn

Approval Date: May 1, 2007

Indications: For extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to reduce the recurrence of VTE in patients with cancer.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pharmacia & Upjohn
Attention: Robert B. Clark
Vice President, U.S. Regulatory Strategy
Agent for Pharmacia & Upjohn Company
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

We acknowledge receipt on March 1, 2007 of your February 28, 2007 resubmission to your supplemental new drug application for Fragmin® (dalteparin sodium injection).

Please refer to your supplemental new drug application dated March 16, 2004, received March 17, 2004, 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 February 28, April 26, 27 (2) and April 30, 2007 (4).

Your submission of February 28, 2007 constituted a complete response to our March 14, 2006 action letter.

This supplemental new drug application provides for the use of Fragmin® (dalteparin sodium injection) for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to reduce the recurrence of VTE in patients with cancer.

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 and with the minor editorial revision listed below.

Include the revisions to the blister labeling and carton container labeling in the respective colors at your next printing.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (text for the package insert, immediate container and carton labels) and submitted labeling (package insert submitted April 30, 2007, immediate container labels submitted April 27, 2007, blister labeling submitted April 30, 2007, and carton labels submitted April 30, 2007).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-287/S-035.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies until May 1, 2010.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

We remind you of your postmarketing study commitments in your submission dated April 27, 2007. These commitments are listed below.

1. To evaluate efficacy and safety of dalteparin in pediatric cancer patients. Studies using dalteparin for venous thromboembolism (VTE) treatment in all age ranges of the pediatric population should be performed.

Protocol Submission:	Within 6 months of the date of this letter.
Study Start:	Within 18 months of the date of this letter.
Final Report Submission:	Within 36 months of the date of this letter.

   Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments.**"

2. To conduct a study to evaluate the safety and efficacy of dalteparin in cancer patients (both metastatic and non-metastatic) receiving extended treatment with dalteparin (>6 months) for prevention of new or recurrent symptomatic venous thromboembolism (VTEs), including subjects with renal impairment (including severe renal impairment).

Protocol Submission:	Within 6 months of the date of this letter.
Study Start:	Within 18 months of the date of this letter.
Final Report Submission:	Within 60 months of the date of this letter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Mrs. Diane Leaman, Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Acting Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure
Fragmin®
dalteparin sodium injection

For *Subcutaneous* Use Only

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/s/

Rafel Rieves
5/1/2007 04:11:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

2nd cycle

NDA 20-287/S-035

Pharmacia & Upjohn
Attention: Robert B. Clark
Vice President, Pfizer, Inc.
Acting Agent for Pharmacia & Upjohn
235 East 42nd St.
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug application dated March 16, 2004, received March 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium, injection) 2500 IU, 5000 IU, 7500 IU, 10,000 IU and 25,000 IU.

We acknowledge receipt of your submissions dated January 18, 21, March 15, 25, April 6, and September 14, 2005; February 17 and March 1, 2006.

Your submission of September 14, 2005, constituted a complete response to our January 14, 2005 action letter.

This supplemental new drug application proposes the use of Fragmin® (dalteparin sodium, injection) for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer.

We completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. The submitted clinical data do not provide sufficient evidence of the safety of dalteparin for the proposed indication. Specifically, the supplied data do not rule out a clinically important association of dalteparin with a mortality disadvantage when compared to oral anticoagulation. The basis for this concern is summarized below.

2. The major source of clinical data supporting the safety and efficacy of dalteparin for the proposed indication is derived from the clinical study entitled, "Randomized comparison of low molecular weight heparin (dalteparin, Fragmin) versus oral anticoagulant therapy for long-term anticoagulation in cancer patients with venous thromboembolism." This study is referred to as the "CLOT" study. In this study, 677 patients were randomized to either the study agent group (dalteparin) or the control group (oral anticoagulant, OAC). The study agent regimens, administered in an open label manner, were supposed to extend over a six month period for both study groups.

a. Compliance with the proposed treatment duration was very limited for both study groups. Specifically, approximately 50% of the randomized patients completed the assigned study drug regimens. Patients and investigators discontinued the assigned drug regimens for a variety of reasons, including certain subjectively determined reasons as well as the occurrence of death and adverse events.

b. The study's primary endpoint result, time to first recurrence of a symptomatic venous thromboembolic event (VTE), was the finding of a statistically significant treatment effect for patients in the dalteparin group.

c. The major safety finding related to an excess in study drug discontinuations due to death in the dalteparin group (17.5%) compared to the OAC group (6.3%). Other safety observations related to numerically higher rates of major bleeding and thrombocytopenia among patients in the dalteparin group.

d. The excess of patients in the dalteparin group who discontinued the assigned study drug regimen due to death provides evidence that dalteparin may have contributed to an excess in "on treatment" mortality even though the overall cumulative mortality rates were similar between the two study groups. Analyses that attempt to adjust for the "time on treatment" do not resolve the imbalance in the rates of study drug regimen discontinuation due to death. These data and analyses provide evidence that dalteparin may have contributed to an excess of deaths in the cancer patient population.

e. The rates of the "on treatment" deaths are similar to those for the rates of the first VTE recurrence and raise the possibility that the study's primary endpoint result may have been confounded by the imbalance in "on treatment" deaths.

3. Review of the CLOT study has identified a serious safety concern of excess deaths "on treatment" in the dalteparin arm as compared to the OAC group that cannot be resolved with additional analyses of data from the study. We note that a published medical practice guideline (Chest 2004: supplement number 3, page 411S) cites the CLOT study to support the use of your study agent "for most patients with DT and cancer." However, this publication does not describe the "on treatment" safety concern detected in the study. Another publication of the CLOT study findings (NEJM 2003; 349:146-53) also does not describe the "on treatment" safety concern detected in the study. These observations suggest that public disclosure of the safety findings from the CLOT study is limited. Please describe your plans for addressing this concern.

To gain approval for the proposed indication, you must provide definitive evidence of the safety and efficacy of dalteparin to support the proposed indication. While alternatives to the recommendations outlined below will be considered, we recommend that you:

1. Design and conduct at least one additional adequate and well-controlled clinical study that enrolls a broad population of cancer patients. This study should be designed to provide definitive clinical evidence of dalteparin efficacy for the proposed indication and to thoroughly evaluate the safety of the drug, especially with respect to mortality. The study should employ stringent methods to minimize bias (i.e., blinding, double-double dummy control, use of sham INRs), especially with respect to the reasons for discontinuation of the assigned study drug regimen. The proposed indication's target population should be enrolled (i.e., the broad population of cancer patients with

VTE). Because the CLOT study showed inconsistent primary endpoint results among patients with supposedly non-metastatic cancer and patients with hematologic cancers, consideration should be given to stratifying for these baseline observations. The study protocol should be submitted for review.

2. Design and conduct an adequate and well-controlled study of sufficient size to provide evidence of the efficacy and safety of dalteparin for the proposed indication in the sub-population of cancer patients with a non-metastatic cancer or a history of a non-metastatic cancer at baseline. The study protocol should be submitted for review.

3. Obtain clinical evidence to describe the safe and effective use of dalteparin for the proposed indication among cancer patients with renal impairment. We note that the limited clinical data submitted from patients with renal impairment (especially moderate-to-severe impairment) appear insufficient to evaluate the drug's effects in patients with cancer and renal impairment and to address considerations of dosage alteration due to renal failure. The current dalteparin labeling indicates that the drug may accumulate in patients with renal failure requiring hemodialysis. Consequently, unique safety considerations may occur among cancer patients with renal impairment, especially renal failure. Lack of these data or limitations of these data may necessitate explicit notations within the proposed label.

4. Propose a clinical development plan to investigate efficacy and safety of dalteparin in pediatric cancer patients who require anticoagulation. Accordingly, although the incidence of pediatric cancer patients with VTE is small, these, and other pediatric populations, do experience VTEs and require anticoagulation. Therapeutic options are needed for these patients. We strongly recommend that you propose a development plan to investigate efficacy and safety of dalteparin in pediatric patients who require anticoagulation.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

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/s/

George Mills
3/14/2006 05:21:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

1st cycle

NDA 20-287/S-035

Robert B. Clark
Vice President, Pfizer Inc.
Agent for Pharmacia & Upjohn
235 E 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug application dated March 16, 2004, received March 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium, injection) 2500 IU, 5000 IU, 10,000 IU, 25,000 IU and 7500 IU.

We acknowledge receipt of your submissions dated March 25, May 13, July 29, September 20, November 1, December 17, 23, 2004; January 5, 6 and 13, 2005.

This supplemental new drug application provides for the use of Fragmin® (dalteparin sodium, injection) for extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)] to reduce recurrent VTE in patients with cancer.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

Provide summary and analysis by treatment duration and Fragmin dose of data from the Fragmin safety database, including evaluations of hepatic transaminases, bilirubin and other measures of liver function to assess safety of dalteparin at the doses and for the duration proposed for the indication being sought. To more accurately assess possible risk, information on higher doses and longer treatment durations from studies where patients are not chronically ill should be summarized separately from information from chronically or severely ill patients. Commit to conduct the following post-marketing studies:

1. A safety and efficacy study with FRAGMIN compared to an oral anticoagulant for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with cancer who have varying degrees of renal impairment.

2. A safety and efficacy study with Fragmin compared to an oral anticoagulant for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with hematologic malignancies.

3. A safety and efficacy study with Fragmin compared to an oral anticoagulant for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with non metastatic tumors.

4. A plan to address the use of Fragmin for the extended treatment of symptomatic VTE in pediatric patients.

In addition, you should consider further studies to investigate how best to transition patients from Fragmin to oral anticoagulation (OAC), should that change in therapy become necessary for a patient. The CLOT study data suggest and you have discussed that patients being transitioned to OAC may be inadequately protected against recurrent thrombosis, due to pharmacodynamic issues related to time course of depletion of Vitamin K dependent coagulation factors and Proteins C and S.

In addition, you must submit draft labeling revised as indicated in the attached labeling. Note that in some areas of the labeling we have indicated that you should update information and provide revisions for clarity.

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

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

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

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

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

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

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Gastrointestinal and Coagulation Drug Products to discuss what further steps need to be taken before the application may be approved.

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

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

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

25 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Kathy Robie-Suh
1/18/05 10:03:17 AM
Signing for Dr. Joyce Korvick. Paper copy signed on 1/14/2005.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

LABELING

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

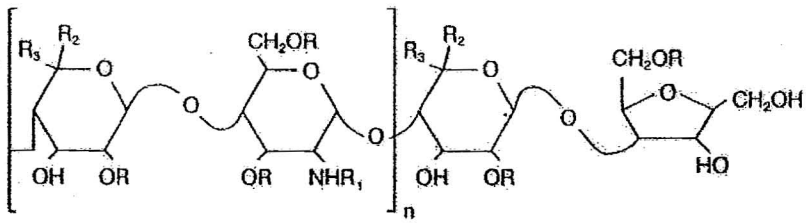
FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes preassembled with a needle guard device, and multiple-dose vials. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each syringe contains either 2500, 5000, 7500, 10,000, 12,500, 15,000 or 18,000 anti-Factor Xa international units (IU), equivalent to 16, 32, 48, 64, 80, 96 or 115.2 mg dalteparin sodium, respectively. Each multiple-dose 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%
3000 to 8000 daltons	65.0 - 78.0%
> 8000 daltons	14.0 - 26.0%

Structural Formula



CLINICAL PHARMACOLOGY

Dalteparin is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In man, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting the 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 twice daily 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/every 12 hr s.c. n (%)	**Placebo** every 12 hr s.c. n (%)
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 to 3. 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 once daily[1] s.c. n (%)	**Warfarin Sodium** once daily[2] oral n (%)
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. three times a day 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 to 3. 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 once daily s.c. n (%)	**Placebo** Once daily s.c. n (%)
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 once daily s.c. n (%)	**Heparin** 5000 U twice daily s.c. n (%)
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 once daily s.c. n (%)	**FRAGMIN** 5000 IU once daily s.c. n (%)

All Treated Abdominal Surgery Patients[1]	696	679
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	99/656 (15.1)[2]	60/645 (9.3)
Proximal DVT	18/657 (2.7)	14/646 (2.2)
Distal DVT	80/657 (12.2)	41/646 (6.3)
PE		
Fatal	1/674 (0.1)	1/669 (0.1)
Non-fatal	2	4

[1] Major abdominal surgery with malignancy

[2] p-value = 0.001

Prophylaxis of Deep Vein Thrombosis in Medical Patients at Risk for Thromboembolic Complications Due to Severely Restricted Mobility During Acute Illness

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

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

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

Indication	Dosing Regimen	
	FRAGMIN 5000 IU once daily s.c. n (%)	**Placebo** Once daily s.c. n (%)
All Treated Medical Patients During Acute Illness	1848	1833
Treatment failure in evaluable patients (Day 21)[1]		
DVT, PE, or sudden death	42/1518 (2.8)[2]	73/1473 (5.0)

Total thromboembolic events (Day 21)	37/1513 (2.5)	70/1470 (4.8)
Total DVT	32/1508 (2.1)	64/1464 (4.4)
Proximal DVT	29/1518 (1.9)	60/1474 (4.1)
Symptomatic VTE	10/1759 (0.6)	17/1740 (1.0)
PE	5/1759 (0.3)	6/1740 (0.3)
Sudden Death	5/1829 (0.3)	3/1807 (0.2)

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

Patients with Cancer and Acute Symptomatic Venous Thromboembolism

In a prospective, multi-center, open-label, clinical trial, 676 patients with cancer and newly diagnosed, objectively confirmed acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were studied. Patients were randomized to either Fragmin 200 IU/kg (max 18,000 IU/ s.c. daily for one month) then 150 IU/kg (max 18,000 IU s.c. daily) for five months (FRAGMIN arm) or FRAGMIN 200 IU/kg (max 18,000 IU s.c. daily) for five to seven days and oral anticoagulant for six months (OAC arm). In the OAC arm, oral anticoagulation was adjusted to maintain an INR of 2 to 3. Patients were evaluated for recurrence of symptomatic venous thromboembolism (VTE) every two weeks for six months.

The median age of patients was 64 years (range: 22 to 89 years); 51.5% of patients were females; 95.3% of patients were Caucasians. Types of tumors were: breast (16%), lung (13.3%), gastrointestinal tract (23.7%), genito-urinary (21.5%), hematological tumors (10.4%) or other tumors (15.1%). Venous thrombotic events were adjudicated by a blinded central committee.

A total of 27 (8.0%) and 53 (15.7%) patients in the FRAGMIN and OAC arms, respectively, experienced at least one episode of an objectively confirmed, symptomatic DVT and/or PE during the 6-month study period. Most of the difference occurred during the first month of treatment (see Table 7). The benefit was maintained over the 6-month study period.

Table 7
Recurrent VTE in Patients with Cancer (Intention to treat population)[1]

Study Period	FRAGMIN arm			OAC arm		
	FRAGMIN 200 IU/kg (max. 18,000 IU) s.c. once daily x 1 month, then 150 IU/kg (max. 18,000 IU) s.c. once daily x 5 months			FRAGMIN 200 IU/kg (max 18,000 IU) s.c. once daily x 5 to 7 days and OAC for 6 months (target INR 2.0-3.0 2 to 3)		
	Number at Risk	Patients with VTE	%	Number at Risk	Patients with VTE	%
Total	338	27	8.0	338	53	15.7
Week 1	338	5	1.5	338	8	2.4
Week 2-4	331	6	1.8	327	25	7.6
Weeks 5-28	307	16	5.2	284	20	7.0

[1] Three patients in the FRAGMIN arm and 5 patients in the OAC arm experienced more than 1 VTE over the 6-month study period.

In the intent-to-treat population that included all randomized patients, the primary comparison of the cumulative probability of the first VTE recurrence over the 6-month study period was statistically significant (p=0.0017) in favor of the FRAGMIN arm, with most of the treatment difference evident in the first month.

INDICATIONS AND USAGE

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

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

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

FRAGMIN is also indicated for the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer.

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 antiplatelet antibody in the presence of FRAGMIN.

Patients undergoing regional anesthesia should not receive FRAGMIN for unstable angina or non-Q-wave myocardial infarction, and patients with cancer undergoing regional anesthesia should not receive FRAGMIN for extended treatment of symptomatic VTE, due to an increased risk of bleeding associated with the dosage of FRAGMIN recommended for these indications.

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 FRAGMIN clinical trials in non-cancer populations, platelet counts of $< 100{,}000/mm^3$ and $< 50{,}000/mm^3$ occurred in < 1% and < 1% of patients, respectively.

In the clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated for up to 6 months in the Fragmin treatment arm, platelet counts of $< 100{,}000/mm^3$ occurred in 13.6% of patients, including 6.5% who also had platelet counts less than $50{,}000/mm^3$. In the same clinical trial, thrombocytopenia was reported as an adverse event in 10.9% of patients in the FRAGMIN arm and 8.1% of patients in the OAC arm. Fragmin dose was decreased or interrupted in patients whose platelet counts fell below $100{,}000/mm^3$.

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. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed.

Miscellaneous

Each 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 be used with caution in pregnant women and only if clearly needed. If anticoagulation with FRAGMIN is needed during pregnancy, preservative-free formulations should be used, where possible. (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, blood chemistry, and stool occult blood tests are recommended during the course of treatment with FRAGMIN. No special monitoring of blood clotting times (i.e., 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 the anticoagulant effect of FRAGMIN.

Anti-Factor Xa may be used to monitor the anticoagulant effect of FRAGMIN, such as in patients with severe renal impairment or if abnormal coagulation parameters or bleeding should occur during FRAGMIN therapy.

Drug/Laboratory Test Interactions

Elevations of Serum Transaminases

In Fragmin clinical trials supporting non-cancer indications where hepatic transaminases were measured, asymptomatic increases in transaminase levels (SGOT/AST and SGPT/ALT) greater than three times the upper limit of normal of the laboratory reference range were seen in 4.7% and 4.2%, respectively, of patients during treatment with FRAGMIN.

In the FRAGMIN clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated with Fragmin for up to 6 months, asymptomatic increases in transaminase levels, AST and ALT, greater than three times the upper limit of normal of the laboratory reference range have been were reported in 8.9% and 9.5% of patients, respectively. The frequencies of Grades 3 and 4 increases in AST and ALT, as classified by the National Cancer Institute, Common Toxicity Criteria (NCI-CTC) Scoring System, were 3% and 3.8%, respectively. Grades 2, 3 & 4 combined have been reported in 12% and 14% of patients, respectively.

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 and the 3.8 mL multiple-dose vials of FRAGMIN contain 14 mg/mL of benzyl alcohol.

Nursing Mothers

Limited data are available for excretion of dalteparin in human milk. One study in 15 lactating women receiving prophylactic doses of dalteparin detected small amounts of anti-Xa activity in breast milk, equivalent to a milk/plasma ratio of <0.025-0.224. As oral absorption of LMWH is extremely low, the clinical implications, if any, of this small amount of anticoagulant activity on the nursing infant are unknown. Caution should be exercised when Fragmin is administered to nursing women.

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, 5516 patients were 65 years of age or older and 2237 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 8 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

Table q
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] n (%)	**Heparin** i.v. and s.c.[2] n (%)	**Placebo** every 12 hr s.c. n (%)
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, APTT 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 9 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 9
Bleeding Events Following Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	**FRAGMIN** 5000 IU once daily s.c. n (%)	**Warfarin** Sodium[1] oral n (%)	**FRAGMIN** 5000 IU once daily s.c. n (%)	**Heparin** 5000 U three times daily s.c. n (%)
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 10 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients.

Table 10
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 once daily s.c. n (%)	**Heparin** 5000 U twice daily s.c. n (%)	**FRAGMIN** 5000 IU once daily s.c. n (%)	**Heparin** 5000 U twice daily s.c. n (%)	**FRAGMIN** 2500 IU once daily s.c.	**Placebo** once daily s.c. n (%)	**FRAGMIN** 2500 IU once daily s.c. n (%)	**FRAGMIN** 5000 IU once daily s.c. n (%)
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	2/392	3/392	4/508	2/498	1/79	1/78	2/1030	13/1038

Due to Bleeding	(0.5)	(0.8)	(0.8)	(0.4)	(1.3)	(1.3)	(0.2)	(1.3)
Injection Site Hematoma	1/466 (0.2)	5/464 (1.1)	36/506 (7.1)	47/493 (9.5)	8/172 (4.7)	2/174 (1.1)	36/1026 (3.5)	57/1035 (5.5)

Medical Patients with Severely Restricted Mobility During Acute Illness

Table 11 summarizes major bleeding events that occurred in a clinical trial of medical patients with severely restricted mobility during acute illness.

Table 11
Bleeding Events in Medical Patients with Severely Restricted Mobility During Acute Illness

Indication	Dosing Regimen	
Medical Patients with Severely Restricted Mobility	**FRAGMIN** 5000 IU once daily s.c. n (%)	**Placebo** once daily s.c. n (%)
Major Bleeding Events[1] at Day 14	8/1848 (0.4)	0/1833 (0)
Major Bleeding Events[1] at Day 21	9/1848 (0.5)	3/1833 (0.2)

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

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

Patients with Cancer and Acute Symptomatic Venous Thromboembolism

Table 12 summarizes the number of patients with bleeding events that occurred in the clinical trial of patients with cancer and acute symptomatic venous thromboembolism. A bleeding event was considered major if it: 1) was accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical symptoms; 2) occurred at a critical site (intraocular, spinal/epidural, intracranial, retroperitoneal, or pericardial bleeding); 3) required transfusion of ≥ 2 units of blood products; or 4) led to death. Minor bleeding was classified as clinically overt bleeding that did not meet criteria for major bleeding.

At the end of the six-month study, a total of 46 (13.6%) patients in the FRAGMIN arm and 62 (18.5%) patients in the OAC arm experienced any bleeding event. One bleeding event (hemoptysis in a patient in the FRAGMIN arm at Day 71) was fatal.

Table 12
Bleeding Events (Major and Any) (As treated population)[1]

Study period	FRAGMIN 200 IU/kg (max. 18,000 IU) s.c. once daily x 1 month, then 150 IU/kg (max. 18,000 IU) s.c. once daily x 5 months			OAC FRAGMIN 200 IU/kg (max 18,000 IU) s.c. once daily x 5-7 days and OAC for 6 months (target INR 2 to 3)		
	Number at risk	Patients with Major Bleeding n (%)	Patients with Any Bleeding n (%)	Number at risk	Patients with Major Bleeding n (%)	Patients with Any Bleeding n (%)
Total during study	338	19 (5.6)	46 (13.6)	335	12 (3.6)	62 (18.5)
Week 1	338	4 (1.2)	15 (4.4)	335	4 (1.2)	12 (3.6)
Weeks 2-4	332	9 (2.7)	17 (5.1)	321	1 (0.3)	12 (3.7)
Weeks 5-28	297	9 (3.0)	26 (8.8)	267	8 (3.0)	40 (15.0)

[1]Patients with multiple bleeding episodes within any time interval were counted only once in that interval. However, patients with multiple bleeding episodes that occurred at different time intervals were counted once in each interval in which the event occurred.

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 once daily vs 11.8% of patients treated with heparin 5000 IU twice daily 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 once daily vs 13% of patients treated with heparin 5000 U three times a day.

Ongoing Safety Surveillance

Since first international market introduction in 1985, there have been more than 15 reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. The majority of patients had postoperative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. In some cases the hematoma resulted in

long-term or permanent paralysis (partial or complete). Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Post-Marketing Experience

Skin necrosis has occurred rarely. There have been isolated cases of alopecia reported that improved on drug discontinuation.

OVERDOSAGE

Symptoms/Treatment

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

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

DOSAGE AND ADMINISTRATION

Prophylaxis of Ischemic Complications in 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 13 lists the volume of FRAGMIN, based on the 9.5 mL multiple-dose vial (10,000 IU/mL), to be administered for a range of patient weights.

Table 13
Volume of FRAGMIN to be Administered by Patient Weight, Based on 9.5 mL Vial (10,000 IU/mL)

Patient weight (lb)	< 110	110 to 131	132 to 153	154 to 175	176 to 197	≥198

Patient weight (kg)	< 50	50 to 59	60 to 69	70 to 79	80 to 89	≥90
Volume of FRAGMIN (mL)	0.55	0.65	0.75	0.90	1.0	1.0

Prophylaxis of Venous Thromboembolism Following Hip Replacement Surgery

Table 14 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 14
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 once daily
Preoperative Start - Day of Surgery	---	2500 IU	2500 IU[3]	5000 IU once daily
Preoperative Start - Evening Before Surgery[4]	5000 IU	---	5000 IU	5000 IU once daily

[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.

Prophylaxis of Venous Thromboembolism Following Abdominal Surgery

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

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

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

Medical Patients with Severely Restricted Mobility During Acute Illness

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

Extended Treatment of Symptomatic Venous Thromboembolism in Patients with Cancer

In patients with cancer and symptomatic venous thromboembolism, the recommended dosing of FRAGMIN is as follows: for the first 30 days of treatment administer FRAGMIN 200 IU/kg total body weight subcutaneously (s.c.) once daily. The total daily dose should not exceed 18,000 IU. Table 15 lists the dose of FRAGMIN to be administered once daily during the first month for a range of patient weights.

Month 1

Table 15
Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during the First Month

Body Weight (lbs)	Body Weight (kg)	FRAGMIN Dose (IU) (prefilled syringe) once daily
≤ 124	≤ 56	10,000
125 to 150	57 to 68	12,500
151 to 181	69 to 82	15,000
182 to 216	83 to 98	18,000
≥ 217	≥ 99	18,000

Months 2 to 6

Administer FRAGMIN at a dose of approximately 150 IU/kg, s.c. once daily during Months 2 through 6. The total daily dose should not exceed 18,000 IU. Table 16 lists the dose of FRAGMIN to be administered once daily for a range of patient weights during months 2-6.

Table 16
Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during Months 2-6

Body Weight (lbs)	Body Weight (kg)	FRAGMIN Dose (IU) (prefilled syringe) once daily
≤ 124	≤ 56	7,500
125 to 150	57 to 68	10,000
151 to 181	69 to 82	12,500
182 to 216	83 to 98	15,000
≥ 217	≥ 99	18,000



Manufactured for
Eisai Inc.
Teaneck, NJ 07666



Manufactured by
Pfizer Inc
New York, NY 10017
Made in Belgium
(multiple-dose vials)

Jointly manufactured by
Pfizer Inc, New York, NY 10017
and Vetter Pharma-Fertigung, GmbH & Co. KG
Ravensburg, Germany
(prefilled syringes)

LAB-0058-8.5
Revised April 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

MEDICAL REVIEW(S)

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

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-287
Sponsor:	Pfizer 235 East 42nd St. New York, NY 10017
Drug name:	Fragmin (Dalteparin)
Indication:	Extended treatment of Symptomatic Venous Thromboembolism in Cancer Patients
Route of Administration:	Subcutaneous
Submission:	SE1 035 AZ (Class 1 Resubmission)
Date submitted:	February 28, 2007
Review assigned:	March 7, 2007
Review completed:	April 12, 2007
Reviewer:	Andrew Dmytrijuk, MD

I. Background

Fragmin is a low molecular weight heparin which was approved on December 22, 1994 for use in prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery who are at risk of thromboembolic complications. On March 16, 2004 the sponsor submitted Supplement-035 to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE) to prevent recurrent VTE in patients with cancer. The submission was supported mainly by one study entitled "Randomized Comparison of Low Molecular Weight Heparin Versus Oral Warfarin Therapy for Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism" also known as the CLOT study. The proposed dosage is 200 IU/kg (maximum 18,000 IU) subcutaneously once daily for one month then 150 IU/kg (maximum 18,000 IU) subcutaneously once daily for an additional five months. The first cycle review of this submission was completed by Dr. Andrew Dmytrijuk on January 14, 2005. The supplement was given an approvable action on January 14, 2005 and required that the sponsor provide a summary and analysis by treatment duration and Fragmin dose of data from the Fragmin safety database, including evaluations of hepatic transaminases, bilirubin and other measures of liver function to assess the safety of Fragmin at doses and for the duration proposed for the indication being sought. In addition, the sponsor was to commit to post-marketing studies assessing the safety and efficacy of Fragmin compared to oral anticoagulant for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with cancer who have varying degrees of renal impairment; hematologic malignancies; non-metastatic tumors and to address the use of Fragmin for the extended treatment of symptomatic VTE in pediatric patients. The sponsor provided a full response to the letter on September 15, 2005. The second cycle review of this submission was completed March 8, 2006. The sponsor was issued a "Not Approvable" letter for the supplement on March 14, 2006 citing as the major deficiencies:

- The data did not provide sufficient evidence of the safety of Fragmin for the proposed indication. Specifically the supplied data did not rule out a clinically important association of Fragmin with a mortality disadvantage when compared to oral anticoagulation due to the open label design of the study.
- Compliance with the proposed treatment duration was limited. Approximately 50% of the randomized patients completed the assigned study drug regimens.
- The major safety finding related to an excess in study drug discontinuations due to death in the Fragmin group (17.5%) compared to the oral anticoagulant group (6.3%). Other safety observations related to numerically higher rates of major bleeding and thrombocytopenia among patients in the Fragmin group.

- The excess of patients in the Fragmin group who discontinued the assigned study drug regimen due to death provided evidence that Fragmin may have contributed to an excess in "on treatment" mortality even though the overall cumulative mortality rates were similar between the two study groups.
- The rates of "on treatment" deaths were similar to those for the rates of first VTE recurrence and raised the possibility that the study's primary endpoint result may have been confounded by the imbalance in "on treatment" deaths.

On September 6, 2006 the Division of Medical Imaging and Hematology Drug Products (DMIHP) presented the review of this submission to the Oncologic Drugs Advisory Committee (ODAC) on September 6, 2006. At this meeting the division presented these concerns and in particular its concern regarding the disparity of all cause mortality between the Fragmin arm (59/338, 17%) and the control arm (21/335, 6%) of the study which occurred while patients were on Fragmin therapy. Overall there were 131/338, 39% deaths in the Fragmin arm compared to 137/335, 41% deaths in the control arm during the six-month study period. The ODAC did not regard the study drug discontinuation due to death finding as sufficient to preclude the approval of the application until the issue was resolved with additional clinical studies. The ODAC unanimously recommended approval of the sponsor's proposed indication.

In this submission the sponsor responds to the "Not Approvable" letter dated March 14, 2006. The sponsor states that consistent with the ODAC recommendation that the totality of the CLOT study's safety and efficacy results provide a benefit to risk relationship sufficient to warrant approval of this supplemental marketing application, the sponsor maintains their position that the results of the CLOT study demonstrate that for patients with cancer in symptomatic VTE extended treatment with Fragmin significantly reduces the recurrence of VTE compared to oral anticoagulant and has a favorable risk/benefit profile. Based on this conclusion the sponsor submits revised product labeling.

A review of the safety update (covering October 31, 2003 to July 17, 2004) was completed by Dr. Andrew Dmytrijuk as part of the S-035 NDA review. This review revealed no new safety concerns for Fragmin at that time. On September 14, 2005 a safety update was provided by the sponsor that included safety information from the sponsor's clinical trials completed between October 31, 2003 and March 15, 2005 in order to support the S-035 submission. In the March 14, 2006 "Not Approvable" letter the FDA requested that the sponsor provide another safety update which included data from all non-clinical and clinical Fragmin studies regardless of indication, dosage form or dose level since the previous safety update. In the current submission the sponsor provides an update of the worldwide Fragmin database for any sponsor supported clinical trial that had completed after the safety cutoff date for the last safety update, i.e. March 15, 2005 and the new cutoff date set as March 15, 2006. During this time period no

new clinical studies were identified that investigated the use of Fragmin in the proposed indication. The sponsor provides an update of safety information for five studies that were completed during this time period that had indications different from the current proposed indication:

- Use of Fragmin for VTE prophylaxis in medical patients in the primary care setting
- Use of Fragmin for VTE prophylaxis in patients undergoing total knee replacement
- Use of Fragmin for VTE prophylaxis in patients with ischemic cerebral infarction
- Use of Fragmin for VTE prophylaxis in patients with diabetic nephropathy
- An analysis of the pharmacokinetics of Fragmin in patients with renal insufficiency.

In addition, the sponsor provides a table of adverse events for these studies. The number and types of adverse events are similar to what is currently listed in the adverse events in Fragmin Label.

The sponsor reports that the total number of patients using Fragmin between March 2005 and March 2006 was (b) (4) in the United States with an additional (b) (4) patients using Fragmin outside of the United States. The total number of units dispensed in the United Sates was estimated to be over (b) (4) with over (b) (4) units dispensed outside the United States. From March 2005 to March 2006 the sponsor reports that there were 317 cases reported to the sponsor's early alert safety program. Of the 317 cases, 26 cases were reported as deaths. The sponsor states that the rate of (b) (4) of deaths reported during March 2005 to March 2006 to the early alert program is similar to the 12.5% mortality rate previously reported for the time period October 2003 to March 2005. There were ten cases of death related to hemorrhage from the period of March 2005 to March 2006. Thrombocytopenia was reported in 19 of the 317 cases. Renal failure was reported in 2 of the 317 cases. A review of the provided safety update for the Period of March 2005 to March 2006 reveals no new safety concerns.

In addition, in this submission the sponsor proposes two post marketing clinical studies as post marketing commitments. The sponsor states that one study will assess the safety of Fragmin administration for periods of time in excess of six months. The sponsor proposes that this study will also assess the safety of Fragmin use in patients with cancer and renal impairment including severe renal impairment. The sponsor states that the second study will assess the safety and efficacy of Fragmin in pediatric patients with cancer who require anticoagulation. The sponsor provides protocol synopses for these proposed studies.

II. Conclusions

A revision of the product label proposed by the sponsor is attached in appendix 1 of this review. The DMIHP proposed deletions are stricken through and additions are double underlined. The indication sought by the sponsor for the treatment of symptomatic VTE and to reduce the frequency of recurrent VTE in patients with cancer should be approved using Fragmin in the above stated dosing regimen.

A review of the provided safety update reveals that no new clinical studies were identified during this time period and no new safety concerns are raised by this safety update.

The sponsor should submit the final protocols for the proposed post marketing studies. The first study should assess the safety of Fragmin administration for periods of time in excess of six months and also assess the safety of Fragmin use in patients with cancer and renal impairment including severe renal impairment. The second study should assess the safety and efficacy of Fragmin in pediatric patients with cancer who require anticoagulation and include all ranges of pediatric patients.

III. Recommendations

The indication sought by the sponsor for the extended treatment of symptomatic venous thromboembolism (VTE) to prevent recurrent VTE in patients with cancer should be approved using Fragmin in the above stated dosing regimen.

The sponsor should submit the final protocols for the proposed post marketing studies. The first study should assess the safety of Fragmin administration for periods of time in excess of six months and also assess the safety of Fragmin use in patients with cancer and renal impairment including severe renal impairment. The second study should assess the safety and efficacy of Fragmin in pediatric patients with cancer who require anticoagulation and include all ranges of pediatric patients.

28 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Andrew Dmytrijuk
4/26/2007 04:25:32 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-287
Sponsor:	Pfizer Inc. 235 East 42nd St. New York, NY 10017
Drug name:	Fragmin (Dalteparin Sodium Injection)
Indication:	Extended Treatment of Symptomatic Venous Thromboembolism in Cancer Patients.
Route of Administration:	Subcutaneous
Submission:	S-035, Second Cycle Review
Date submitted:	September 14, 2005; February 17, 2006 and March 1, 2006.
Review assigned:	September 15, 2005
Review completed:	March 8, 2006
Reviewer:	Andrew Dmytrijuk M.D.

I. Executive Summary

Fragmin (dalteparin sodium) is a low molecular weight heparin (LMWH) with antithrombotic properties. The sponsor wishes to add the following indication to the label:

- Extended treatment of symptomatic venous thromboembolism (VTE), i.e., either a proximal DVT and/or PE, to reduce the recurrence of VTE in patients with cancer.

The dose proposed is Fragmin 200 IU/kg total body weight (maximum 18,000 IU) subcutaneously once daily for the first month followed by 150 IU/kg (maximum 18,000 IU) subcutaneously once daily for the next 5 months for a total of 6 months of treatment.

The sponsor initially submitted supplement 035 for NDA 20-287 on March 16, 2004. The first cycle review for this supplement was completed by Dr. Andrew Dmytrijuk on January 14, 2005. A letter was sent to the sponsor indicating that the submission was approvable for the indication being sought on January 14, 2005. In the approvable letter the sponsor was asked to provide:

- A summary and analysis to assess the safety of Fragmin at the doses and for the duration proposed for the indication being sought by treatment duration and Fragmin dose including evaluations of hepatic transaminases, bilirubin and other measures of liver function.
- A safety and efficacy study with Fragmin compared to an oral anticoagulant (OAC) for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with cancer who have varying degrees of renal impairment.
- A safety and efficacy study with Fragmin compared to an OAC for the extended treatment of symptomatic VTE in patients with hematologic malignancies.
- A safety and efficacy study with Fragmin compared to an OAC for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with non-metastatic tumors.
- A plan to address the use of Fragmin for the extended treatment of symptomatic VTE in pediatric patients.

The sponsor was also asked to consider further studies to investigate how best to transition patients from Fragmin to OAC should that change in therapy become necessary for a patient. The sponsor was also asked to submit draft labeling revised as indicated in the approvable letter dated January 14, 2005.

An additional concern, that of a higher treatment discontinuation rate of Fragmin due to mortality compared to OAC was raised during this review. In the CLOT

study there were 59/338, 17% deaths in the Fragmin arm compared to 21/335, 6% deaths in the OAC arm while on treatment.

The sponsor replied to the approvable letter in a submission dated September 14, 2005. Additional responses to information requests regarding the September 14, 2005 submission were submitted on February 17, 2006 and March 1, 2006.

The sponsor's response to concerns regarding Fragmin extended use in cancer patients with renal impairment and in patients with hematologic malignancies is acceptable. The analysis presented by the sponsor indicates that renally impaired cancer patients treated with Fragmin had less recurrent VTE then OAC treated renally impaired cancer patients. The discrepancy between the two treatment arms in patients with hematologic malignancies with recurrent VTE can be explained by differences in subject baseline characteristics and underlying VTE risk factors. The sponsor has also acceptably responded to the issue regarding the transition of patients from Fragmin to OAC.

The sponsor's proposed plan to evaluate pediatric patients using a (b) (4) of Fragmin in children who are at (b) (4) is inadequate. The primary objective of the study is to (b) (4) . The sponsor should propose a new pediatric plan which compares anti-factor Xa levels to VTE treatment efficacy and other clinical outcomes such as bleeding and possible liver toxicity. In addition, this new study in pediatric cancer patients should be limited to those patients with VTE and stratify the patients according to underlying presence or absence of a CVL.

In addition, this review has indicated that there are additional concerns which are nonetheless important for this indication and drug namely:

- The sponsor should address concerns regarding the higher rate of treatment discontinuation due to death in the Fragmin arm compared to the OAC arm. Overall there does not appear to be a difference in the rate of mortality between the two treatment arms over the course of the study and at the 6 month and 12-month time points.
- The sponsor should perform another study which has a double blind, double dummy design with sufficient numbers of patients enrolled to determine the safety and efficacy of Fragmin for the indication being sought. This is due to the fact that the open label design of the study may have had an impact on the rate of discontinuation of Fragmin due to mortality i.e., there were possibly more discontinuations due to death in the Fragmin arm because of a tendency to continue these patients on treatment with Fragmin for a longer period of time compared to OAC. Any studies performed in patients with non-metastatic malignancies for the current indication should be of similar design.

Therefore the submission for this indication is not approvable.

Additional concern is raised due to the fact that the use of Fragmin for this indication has been widely circulated in both peer reviewed and non-peer reviewed publications. The sponsor should address this issue with a public statement that Fragmin is currently not indicated for the extended treatment and prophylaxis of VTE in patients with cancer.

II. Background

Fragmin (dalteparin sodium) is a low molecular weight heparin (LMWH) with antithrombotic properties. Fragmin is currently approved for the following indications:

Fragmin is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy.

Fragmin is also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

The sponsor wishes to add the following indication to the label:

- Extended treatment of symptomatic venous thromboembolism (VTE), i.e., either a proximal DVT and/or PE, to reduce the recurrence of VTE in patients with cancer.

The dose proposed is Fragmin 200 IU/kg total body weight (maximum 18,000 IU) subcutaneously once daily for the first month followed by 150 IU/kg (maximum 18,000 IU) subcutaneously once daily for the next 5 months for a total of 6 months of treatment.

The sponsor initially submitted supplement 035 for NDA 20-287 on March 16, 2004. The first cycle review for this supplement was completed by Dr. Andrew Dmytrijuk on January 14, 2005. A letter was sent to the sponsor indicating that the submission was approvable for the indication being sought on January 14, 2005. In the approvable letter the sponsor was asked to provide summary and analysis by treatment duration and Fragmin dose of from the Fragmin safety database, including evaluations of hepatic transaminases, bilirubin and other measures of liver function to assess safety of Fragmin at the doses and for the duration proposed for the indication being sought. To more accurately assess

possible risk, information on higher doses and longer treatment durations from studies where patients are not chronically ill should be summarized separately from information from chronically or severely ill patients. Also, the sponsor was asked to commit to conduct the following post marketing studies:

- A safety and efficacy study with Fragmin compared to an oral anticoagulant (OAC) for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with cancer who have varying degrees of renal impairment.
- A safety and efficacy study with Fragmin compared to an OAC for the extended treatment of symptomatic VTE in patients with hematologic malignancies.
- A safety and efficacy study with Fragmin compared to an OAC for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with non-metastatic tumors.
- A plan to address the use of Fragmin for the extended treatment of symptomatic VTE in pediatric patients.

The sponsor was also asked to consider further studies to investigate how best to transition patients from Fragmin to OAC should that change in therapy become necessary for a patient. The sponsor was also asked to submit draft labeling revised as indicated in the approvable letter dated January 14, 2005.

In response to this approvable letter the sponsor submitted for a second cycle review an information package dated September 14, 2005. In this package the sponsor attempts to address the bullet points listed above. The sponsor submitted no new studies, however, the sponsor performed post hoc analyses of the information which was submitted for the first cycle review. This information was generated from the CLOT (Randomized Comparison of Low Molecular Weight Heparin Versus Oral Warfarin Therapy for Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism) study (see review by Dr. A. Dmytrijuk dated January 14, 2005). Additional responses to information requests regarding the September 14, 2005 submission were submitted on February 17, 2006 and March 1, 2006.

1. A safety and efficacy study with Fragmin compared to an oral anticoagulant (OAC) for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with cancer who have varying degrees of renal impairment.

The sponsor responded to the request for a study of Fragmin in cancer patients with varying degrees of renal impairment as follows:

The sponsor states that the severity of illness in renally impaired cancer patients combined with recruitment of such patients for oncology treatment protocols, pose a hardship to the feasibility of such a study. Patients with renal impairment

(serum creatinine ≥ 3 times upper limit of normal (ULN)) were to be excluded from the CLOT study. However patients with renal insufficiency less than this were treated as well as those patients who developed renal insufficiency during the course of treatment. The sponsor identified 162/676 patients (24%) in both treatment arms of the CLOT study who had reduced renal function at baseline and 253/676 patients (37%) who had reduced renal function at baseline or during the course of treatment based on estimated CRC L < 60 ml/min using the Cockroft-Gault formula. The sponsor performed a post hoc review of the safety and efficacy results in this population and submitted this information to address the deficiency identified in the approvable letter.

In this analysis renal impairment was defined as CRCL. < 60 ml/min and was further divided into moderate renal impairment if CRCL. ≥ 30 and < 60 ml/min and severe renal impairment if CRC L. < 30 ml/min. Efficacy and safety analyses were performed in a similar fashion to that of the CLOT study. The demographics and baseline variables for the subgroups determined by treatment and renal function are summarized below.

Table 1. Baseline characteristics for the subpopulations determined by treatment and renal impairment.

	Renal Impairment				Normal Renal Function[1]			
	Dalteparin N=74		OAC N=88		Dalteparin N=264		OAC N=250	
	N	%	N	%	N	%	N	%
Age Distribution								
< 65 years	25	33.8	20	22.7	157	59.5	162	64.8
>=65 years	49	66.2	68	77.3	107	40.5	88	35.2
Age Median [Range] (years)	71.0 [31.7-84.6]		73.9 [38.6-89.3]		61.7 [22.0 – 80.6]		61.1 [27.9 – 86.1]	
Weight Median [Range] (kg)	64.0 [39 - 105]		65.0 [40 - 104]		75.5 [41.0 - 132.0]		75.0 [45.128.0]	
Gender								
Male	26	35.1	41	46.6	133	50.4	128	51.2
Female	48	64.9	47	53.4	131	49.6	122	48.8
Performance Status (ECOG) 0	13	17.6	12	13.6	67	25.4	51	20.4
1	27	36.5	38	43.2	108	40.9	112	44.8
2	34	45.9	37	42.0	84	31.8	85	34.0
3	-	-	1	1.1	5	1.9	2	0.8
CRCL: (mL/min) Median [Range] n								
Normal[1] (CRCL≥60)	NA		NA		90.4 [60.0-233.5] 245		92.5[60.2-202.7] 225	
Moderately Reduced (30≤CRCL≤60)	48.5 [31.1-59.5] 65		47.8[31.5-59.7] 82		NA		NA	
Severely Reduced (CRCL < 30)]	27.6 [22.2-29.4] 9		26.5[21.0-29.6] 6		NA		NA	
SRCR: (mg/dL) Median [Range] n								
Normal (SRCR ≤ 1.2)	1.0 [0.6 – 1.2] 35		1.0 [0.7 – 1.2] 45		0.8 [0.3, 1.2] 233		0.8 [0.4, 1.2] 208	
Abnormal (SRCR > 1.2)	1.6 [1.2 - 3.3] 39		1.5 [1.2 – 2.9] 43		1.3 [1.2, 1.4] 12		1.4 [1.2, 2.0] 17	

Source Table A1 and A2.

A total of 2/74 (3%) renal impaired cancer patients compared to 15/88 (17%) renal impaired cancer patients treated with Fragmin experienced at least 1 asymptomatic VTE during the 6 month study period. The comparison of the cumulative probability of VTE recurrence over the 6 month study period between the Fragmin and OAC arms was statistically significant (p=0.01). More renally impaired cancer patients treated with Fragmin (21/87, 24%) compared to OAC treated renally impaired cancer patients (15/74, 20%) experienced at least 1 bleeding episode during the treatment. However this difference was not statistically significant. More Fragmin treated than OAC treated renally impaired cancer patients experienced at least 1 major bleeding event. However the comparison of cumulative probability of major bleeding events for the two treatment arms was not statistically significant. The following table demonstrates the results of the efficacy analysis and safety analysis in terms of first VTE recurrence, any bleeding and major bleeding in cancer patients with renal impairment.

Table 2. Comparison of treatment effects on 1st VTE recurrence (ITT), 1st any bleeding (AST) & 1st major bleeding (AST) in the patients with renal impairment.

Variable	Treatment	# Patients	# Events	# Censored	P-value[1]	Hazard Ratio	Lower Bound 95% CI for HR	Upper Bound 95% CI for HR
VTE	Dalteparin	74	2	72				
(N=162)	OAC	88	15	73	0.0111	0.148	0.034	0.647
Any Bleeding	Dalteparin	74	15	59				
(N=161)	OAC	87	21	66	0.4658	0.781	0.402	1.517
Major Bleeding	Dalteparin	74	7	67				
(N=161)	OAC	87	6	81	0.6511	1.287	0.432	3.834

Source Listing 1.

Therefore, the post hoc analysis presented by the sponsor indicates that renally impaired cancer patients treated with Fragmin had less recurrent VTE then OAC treated renally impaired cancer patients. In addition, although there are numerically more renally impaired cancer patients with any and major bleeding events, these differences were not statistically significant. The response provided by the sponsor appears to be acceptable. A change in the labeling reflecting this information can be seen in the attached draft labeling.

2. A safety and efficacy study with Fragmin compared to an OAC for the extended treatment of symptomatic VTE in patients with hematologic malignancies.

The first cycle review of this submission revealed that in the CLOT study, patients with hematologic malignancies had a higher rate of VTE in the Fragmin arm (4/40, 10%) compared to the OAC arm (0/30, 0%). Other studies have found that patients with hematological malignancies had an increased risk of VTE. In particular, in a 3220 adult patient case-control study (entitled Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis),

the authors found that overall, there was an increased risk and indeed one of the highest risks of VTE associated with hematological malignancies (OR = 26.2, 95% CI = 3.6-191.4).[1] The sponsor responds that the hematologic cancer subpopulation in the CLOT study was too small to draw conclusions about Fragmin's efficacy in that tumor type. The sponsor asserts that the CLOT study was not designed to reach statistically valid conclusions in subpopulation stratified by tumor type. The sponsor has provided a summary of demographics and risk factors at baseline for the CLOT subpopulation with hematologic cancers (see table below). The sponsor states that the two treatment arms for this subpopulation are not balanced and this imbalance may explain the discrepancy in the response to treatment.

Table 1

Subject Characteristics at Baseline for the Hematological Subpopulation

	Dalteparin N=40		OAC N=30		Total N=70	
	N	%	N	%	N	%
Age Distribution						
< 65 years	24.0	60.0	11.0	36.7	35.0	50.0
>=65 years	16.0	40.0	19.0	63.3	35.0	50.0
Age Median [Range] (years)	61.2 [26.1 – 82.5]		70.8 [37.5 – 85.8]		64.7 [26.1 – 85.8]	
Weight Median [Range] (kg)	78.0 [50 - 124]		74.5 [43 - 123]		76.0 [43 - 124]	
Gender						
Male	31	77.5	18	60.0	49	70.0
Female	9	22.5	12	40.0	21	30.0
Performance Status (ECOG)						
0	16	40.0	8	26.7	24	34.3
1	14	35.0	15	50.0	29	41.4
2	6	15.0	6	20.0	12	17.1
3	4	10.0	1	3.3	5	7.1
Tumor Type[+]						
Hematological Tumor	40	100	30	100	70	100
At least One	38	95.0	29	96.7	67	95.7
- Leukemia	8	20.0	4	13.3	12	17.1
- Lymphoma	27	67.5	17	56.7	44	62.9
- Multiple Myeloma	4	10.0	8	26.7	12	17.1
Not Reported	2	5.0	1	3.3	3	4.3
Hematological Tumor Status[++]						
Not in Complete Remission	39	95.1	29	96.7	68	95.8
Complete Remission	2	4.9	1	3.3	3	4.2
Tumor Treatment (last 6 weeks)						
Yes, at least one	35	87.5	22	73.3	57	81.4
Antineoplastic Medication	4	10.0	5	16.7	9	12.9
Palliative Treatment	34	85.0	18	60.0	52	74.3
Radiation	5	12.5	2	6.7	7	10.0
Surgery	.	.	1	3.3	1	1.4
No	5	12.5	8	26.7	13	18.6
Previous Episode of VTE						
DVT Only	3	7.5	4	13.3	7	10.0
PE Only	1	2.5	.	.	1	1.4
Both	1	2.5	.	.	1	1.4
No Previous History of VTE	35	87.5	26	86.7	61	87.1
Qualifying Episode of VTE						
DVT Only	28	70.0	21	70.0	49	70.0
PE Only	9	22.5	7	23.3	16	22.9
Both	3	7.5	2	6.7	5	7.1

[+] Percentage was calculated using the number of subjects with hematologic tumors as denominator. Note that some subjects have more than one hematological tumor.

[++] Percentage was calculated using the number of hematologic tumors as denominator.

	Dalteparin N=40		OAC N=30		Total N=70	
	N	%	N	%	N	%
Transient Risk Factors for VTE						
Major Surgery	4	10.0	2	6.7	6	8.6
Central Venous Catheter	12	30.0	4	13.3	16	22.9
Hospitalization	10	25.0	12	40.0	22	31.4
None of the Above	21	52.5	15	50.0	36	51.4
Continuing Risk Factors for VTE						
Paralysis or Hemiparesis	1	2.5	.	.	1	1.4
Chronic Immobilization	4	10.0	5	16.7	9	12.9
Known Thrombophilia	2	5.0	1	3.3	3	4.3
Strong Family History of VTE	1	2.5	1	3.3	2	2.9
None of the Above	33	82.5	23	76.7	56	80.0
Other Risk Factors for VTE						
Current Alcohol Consumer	22	55.0	10	33.3	32	45.7
Current and/or Former Smoker	22	55.0	16	53.3	38	54.3
Currently Receiving HRT	.	.	1	3.3	1	1.4
Other	2	5.0	1	3.3	3	4.3
None of the Above	11	27.5	10	33.3	21	30.0

The sponsor states that some of the differences in subject baseline characteristics and risk factors between groups may explain some of the discrepancy in response between the two treatment arms namely:

- Poor performance status (Eastern Cooperative Oncology Group (ECOG) score of 3)) was more common in the Fragmin arm (10%) compared to the OAC arm (3%).
- Markers associated with more advanced disease were more common within six weeks of enrollment in the Fragmin arm. These included less use of anti-neoplastic medication and more palliative therapies including radiation.
- Risk factors such as, major surgery and central venous catheters, associated with VTE were more common in the Fragmin arm compared to the OAC arm.
- The Fragmin arm had a higher incidence of patients with lymphomas (27/40) compared to the OAC arm (17/30). The sponsor asserts that lymphoma is the hematologic malignancy associated with the highest risk for VTE.
- There were more current or former smokers in the Fragmin arm compared to the OAC arm.
- There were a higher proportion of males in the Fragmin arm.

The sponsor notes that the only factor which would bias the study results in favor of the Fragmin arm was that in the OAC arm there was a higher median age. However, higher age, in and of itself does not predispose patients to VTE. Therefore, the fact that patients in the OAC arm had a higher median age would not necessarily bias the results of the CLOT study in favor of Fragmin or against Fragmin.

The major risk factors for the 4 patients that had hematologic malignancies and developed VTE can be described as follows:

- Patient 102063 (Fragmin) - This patient is a 58-year-old male with history of chronic lymphocytic leukemia. The patient was a non-smoker with ECOG performance status 2. However, this patient had limited mobility somewhat worse than what is generally accepted to be in this performance range. In addition the patient was on combination chemotherapy with procarbazine and cyclophosphamide.
- Patient 402010 (Fragmin) - This patient is a 60-year-old male with a history of non-Hodgkin's lymphoma which was in partial remission. The patient was a non-smoker who had an ECOG performance status of 2. The patient and did not have recent chemotherapy prior to study randomization. However, this patient died the same day he was randomized. The patient developed a fatal pulmonary embolism which was confirmed on autopsy.
- Patient 501009 (Fragmin) - This patient is a 33-year-old male with history of Hodgkin's disease with an ECOG performance status of 1. The patient was a non-smoker; however, he weighed 107 kg. In addition to this risk factor the patient had recent major surgery and was an inpatient who was undergoing combination chemotherapy with doxorubicin, bleomycin, vinblastine, vincristine and carmustine (BCNU).
- Patient 501016 (Fragmin) - This patient is a 32-year-old male with a history of chronic myeloid leukemia. The patient had no other major risk factors other than he was undergoing treatment with interferon.

The risk factors for the patients listed above and their clinical histories, other than for patient 501016, support the sponsor assessment that the risk factors listed above may explain the discrepancy between the two treatment arms in the CLOT study. However, differences in major risk factors between the 2 groups would have been addressed by the randomization process. Nevertheless, patient 501016 would be the only patient for whom the risk factors that the sponsor indicates may have caused the discrepancies in the two treatment arms were not present. However, this patient was undergoing treatment for an active underlying malignancy at the time of enrollment in the study.

The sponsor further states that a study of Fragmin for this indication, in a hematologic cancer population, would be difficult to perform due to a possible slow enrollment rate which could result in a failure to complete the study. The sponsor states that the enrollment time for the clot study was 31 months to enroll 676 patients, 70 of which had hematologic cancers. In addition, the sponsor asserts that enrollment would be further slowed because patients with hematologic malignancies often choose to enroll in active chemotherapeutic investigations. The sponsor concludes that these difficulties would pose significant problems in completing a well controlled randomized study. Therefore, the sponsor proposes

that the following wording be included in the labeling regarding Fragmin use in patients with hematologic malignancies for the extended treatment of VTE:

- (b) (4) [redacted]

A review of this information provided by the sponsor appears to be acceptable. This study had a slow rate of accrual of patients with hematologic malignancies. A total of 70 patients were enrolled with hematologic malignancies. The CLOT study enrolled the first patient on May 3, 1999 and the last patient completed the study and all follow-up on April 9, 2002. In addition, there was a small number of recurrent VTE events observed in the CLOT study overall (27/338, 8% in the Fragmin arm compared to 53/338, 16% in the OAC arm). It would appear that a study of the indication being sought for this subpopulation of patients with hematologic malignancies would take a long time to complete or would be underpowered. The sponsor further addressed the concern that patients with hematologic malignancies might have an increased major bleeding risk because these are also patients with likely high levels of thrombocytopenia due to underlying problems with hematopoiesis in the submission date February 17, 2006.

The February 17, 2006 submission contains the sponsor's response to the concern for the possibility of increased bleeding risk in patients with hematologic malignancies. The table below shows that the rate of major bleeding over the course of treatment in patients with hematologic malignancies was negligible and similar to that observed in the OAC patients. It is unlikely that patients with hematologic malignancies treated with Fragmin for this indication would be at an increased risk of major bleeding compared to those patients treated with the control arm regimen. These results also support the conclusion that the higher rate of mortality observed in the Fragmin on treatment group compared to the OAC on was not due to, for example, unreported major bleeding.

Table 17.2.2 Major Bleeds by Period: Subjects with Hematologic Cancer (As-Treated Population)

Study Period (Weeks post-treatment)	Dalteparin N=40			OAC N=30		
	Patients with Hematologic Cancer at Risk	Patients With Bleeding	Rate	Patients with Hematologic Cancer at Risk	Patients With Bleeding	Rate
Week 1	40	0	0.0	30	1	3.3
Week 2	38	1	2.6	30	0	0.0
Week 3	37	0	0.0	30	0	0.0
Week 4	37	0	0.0	30	0	0.0
Week 5	36	0	0.0	30	0	0.0
Week 6	35	0	0.0	30	1	3.3
Week 7	32	0	0.0	27	0	0.0
Week 8-11	32	0	0.0	27	0	0.0
Week 12-35	31	0	0.0	25	0	0.0

3. A safety and efficacy study with Fragmin compared to an OAC for the extended treatment of symptomatic VTE to reduce the frequency of recurrent VTE in patients with non-metastatic tumors.

In the CLOT study there were 298/338, 88% of patients with solid tumors in the Fragmin arm compared to 308/338, 91% of such patients in the OAC arm. Of these, 223/338, 66% and 223/338, 69% in the Fragmin and OAC arms, respectively, had stage IV (metastatic) disease. There were 75/338, 22% and 76/338, 22% of patients with stage I (localized disease) to stage III (advanced localized disease) in the Fragmin and OAC arms, respectively. In terms of VTE recurrence in patients with non-metastatic cancer, there were 7/75, 9% and 5/76, 6% patients in the Fragmin and OAC arms, respectively with VTE recurrence. In response, the sponsor states that the original CLOT study design was not powered to quantitatively assess the responses of small subgroups of patients. However, the sponsor proposes a (b) (4)

(b) (4)

This response does not appear to be acceptable. The proposed (b) (4)

4. A plan to address the use of Fragmin for the extended treatment of symptomatic VTE in pediatric patients.

The sponsor responds to this Pediatric Research Equity Act of 2003 (PREA) requirement by (b) (4)

(b) (4)

The sponsor should propose to do a well-controlled randomized study in pediatric cancer patients, stratifying those patients with CVL and excluding those with arterial thromboembolic events, which correlates anti-factor Xa levels with clinical outcomes. The treatment duration should be 6 months.

5. Additional concerns:

A. In the CLOT study there were 59/338, 17% deaths in the Fragmin arm compared to 21/335, 6% deaths in the OAC arm while on treatment as is shown in the table below. There were total of 131/338, 39% deaths in the Fragmin arm compared to 137/335, 41% deaths in the OAC arm overall (combined on treatment and off treatment) during the 6 month study period and this is also shown the table below. There were 4/338, 1% deaths due to fatal VTE in the Fragmin arm compared to 5/335, 2% deaths due to fatal VTE in the OAC arm. There were 1/338, <0.01 percent deaths due to fatal bleeding in the Fragmin arm compared to 0/335, 0% deaths due to fatal bleeding in the OAC arm.

Table 46. Summary of Deaths (As-treated Population)

Primary Cause of Death	Dalteparin N=338						OAC N=335					
	On Treatment		Off treatment		Total		On Treatment		Off treatment		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	59	17.5	131	38.8	190	56.2	21	6.3	173	51.6	194	57.9
Patients with adjudicated reason of death (first 6 months)												
All	59	17.5	72	21.3	131	38.8	21	6.3	116	34.6	137	40.9
Underlying cancer	54	16.0	65	19.2	119	35.2	14	4.2	110	32.8	124	37.0
Fatal PE	4	1.2	2	0.6	6	1.8	5	1.5	3	0.9	8	2.4
Fatal bleeding	1	0.3	2	0.6	3	0.9	0	0.0	1	0.3	1	0.3
Other	0	0.0	3	0.9	3	0.9	2	0.6	2	0.6	4	1.2
Patients without adjudicated reason of death (from 6 to 12 months)												
All	—	—	59	17.5	59	17.5	—	—	57	17.0	57	17.0
Underlying cancer	—	—	45	13.3	45	13.3	—	—	45	13.4	45	13.4
Infection	—	—	5	1.5	5	1.5	—	—	3	0.9	3	0.9
Cardiac disorders	—	—	3	0.9	3	0.9	—	—	0	0.0	0	0.0
Renal disorders	—	—	3	0.9	3	0.9	—	—	1	0.3	1	0.3
Respiratory disorders	—	—	1	0.3	1	0.3	—	—	1	0.3	1	0.3
Fatal bleeding	—	—	0	0.0	0	0.0	—	—	1	0.3	1	0.3
Other	—	—	1	0.3	1	0.3	—	—	3	0.9	3	0.9
Unknown	—	—	1	0.3	1	0.3	—	—	3	0.9	3	0.9

Abbreviations: OAC = oral anticoagulant
Source: Tables T7.13, and T9.7; Appendix 3.6.3

There were 2 patients in the OAC arm who died while on treatment of causes other than underlying malignancy, bleeding or PE. Patient 102055 was a 57-year-old female smoker with an underlying history of chronic obstructive pulmonary disease and locally advanced non-small cell lung cancer. The patient's performance status was ECOG 1. The patient was undergoing radiation therapy to the left hilum and mediastinum along with combination chemotherapy consisting of cisplatin and vinblastine. The patient developed neutropenia

secondary to chemotherapy and died due to overwhelming sepsis as a result of the neutropenia. Patient 203004 is a 75-year-old male with a history of prolymphocytic leukemia. The patient's performance status was ECOG 1. The patient was undergoing combination chemotherapy with vincristine and cyclophosphamide. The patient was found to be hypoxic, hypothermic and unresponsive at home. No further information to determine cause of death is available.

There were 5 patients with either fatal PE or fatal bleeding in the Fragmin arm and 7 patients with either fatal PE or fatal bleeding in the OAC arm. In addition, there were 54/338, 16% deaths due to progression of malignancy in the Fragmin arm compared to 14/335, 4% deaths due to progression of malignancy in the OAC arm while on treatment. The higher overall death rate in the Fragmin arm compared to the OAC arm is concerning. In addition, in the first cycle review it was noted that both treatment arms were well-balanced with regard to ECOG performance status, underlying presence of a solid tumor, stage IV (metastatic) disease presence (see review by Dr. A. Dmytrijuk dated January 14, 2005). Although more patients appear to have died in the Fragmin arm compared to the OAC arm due to progression of malignancy, there is not a clear explanation for the reason why more patients died in the Fragmin arm on treatment compared to the OAC arm on treatment if both arms were well-balanced with regard to malignancy and other malignancy related risk factors as noted above. From the group of patients that died due to underlying cancer in the Fragmin arm, 4/54 patients had progression of their hematologic malignancy and appeared to have died because of this. From the group of patients that died due to underlying cancer in the OAC arm 2/14 had progression of their hematologic malignancy and appeared to have died because of this.

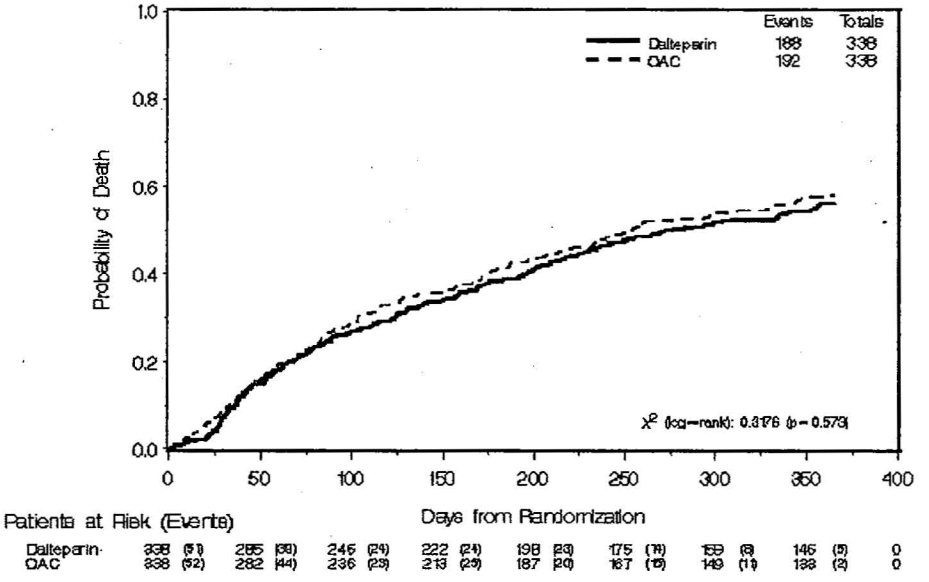
Therefore, there remains a discrepancy between the treatment arms in terms of the on treatment number of patients who died due to underlying cancer with solid tumors (50/54 in the Fragmin arm and 12/14 in the OAC arm). The table below shows the demographic background of the patients in either group. Discrepancies in numbers in any category (other than average time on treatment) for the table below should have been addressed by randomization and therefore are not the underlying reason why there were more deaths in the Fragmin on treatment arm than on the OAC on treatment arm. In the February 17, 2006 and March 1, 2006 submissions the sponsor states that the higher rate of discontinuations due to death in the Fragmin arm compared to the OAC arm was due to the fact that patients in the Fragmin arm were on treatment longer than patients in the OAC arm. However, in the on treatment group with solid tumor malignancies who died, there was only a 1.4 fold increase in the average number of days on treatment in the Fragmin group compared to a 4.2 fold increase in the number of deaths in the Fragmin treated patients with solid tumor malignancies.

On Treatment Solid Tumor Group that Died due to Underlying Malignancy

	Fragmin (n=50)		OAC (n=12)		Total (n=62)	
	n	%	n	%	n	%
VTE Recurrence	1	2	0	0	1	2
Major Bleed	2	4	0	0	2	3
Age < 50	5	10	3	25	8	13
Age ≥ 50 and < 70	32	64	4	33	36	58
Age ≥ 70	13	26	5	42	18	29
Stage I-III	5	10	4	33	9	15
Stage IV	45	90	8	66	53	85
ECOG 0-1	23	46	6	50	29	47
ECOG 2	27	54	6	50	33	53
On Active ChemoRx or XRT	34	68	7	58	41	66
Inpatient Status at VTE Diagnosis	24	48	7	58	31	50
Current Smoker or Quit <1yr	12	24	5	42	17	27
Average Number of Days on Treatment	76		56			
Other Major Illness	12	24	4	33	16	26

However, survival in the CLOT study was estimated at 6 and 12 months after randomization. The cumulative probability of death at both six and 12 months was similar in the two treatment arms (at 6 months the cumulative probability of death was 0.390 in the Fragmin arm and 0.411 in the OAC arm (p=0.20) and at 12 months the cumulative probability of death was 0.561 in the Fragmin arm compared to 0.580 in the OAC arm (p=0.38)). The figure below shows that the time to death overall during the 12 months following randomization was similar between the two treatment arms.

Figure 2. Time-to-Death During the 12 Months Following Randomization - Kaplan-Meier Curves (ITT Population)



The information provided by this figure is reassuring because there does not appear to be a difference in the rate of mortality between the two treatment arms overall. Nevertheless, there remains the concern that there was a higher rate of discontinuation due to death in the on treatment Fragmin group compared to the on treatment OAC group. In a teleconference held with the sponsor on February 7, 2006, the sponsor was asked to provide further analyses in an attempt to better understand the discrepancy between the mortality rates between the treatment arms. Responses to this concern were submitted on February 17, 2006 and March 1, 2006.

In subsequent submissions dated February 17, 2006 and March 1, 2006, the sponsor responded to the recommendations listed above. The sponsor provided the following table which attempts to address the reason why there was a higher mortality rate while on treatment in the Fragmin on treatment group compared to be OAC on treatment group for the intention to treat population.

Table 1.6.1 Crude Death Rates (On-Treatment) at Each Study Period (ITT Population)

Study Period (month)	Dalteparin (N=338)					OAC (N=338)				
	N	# of Subjects On-Treatment	# of Subjects Died*	Total Subject-months**	Crude Death Rate	N	# of Subjects On-Treatment	# of Subjects Died*	Total Subject-months**	Crude Death Rate
<1	338	338	17	315.34	5.39	338	335	11	295.28	3.73
1-2	311	286	15	260.08	5.77	304	262	3	240.66	1.25
2-3	275	238	9	227.99	3.95	270	226	4	210.51	1.90
3-4	249	217	4	211.00	1.90	242	192	3	184.87	1.62
4-5	237	207	9	198.17	4.54	221	180	0	176.47	0.00
5-6	220	192	5	177.60	2.82	211	173	0	160.16	0.00
6-7	206	110	0	12.49	0.00	195	98	0	18.16	0.00
7-8	191	0	0	0.00		181	1	0	0.79	0.00
Total	338	338	59	1402.68	4.21	338	335	21	1286.90	1.63

*Deaths that occur within 1 day of study drug discontinuation are included in the on-treatment death totals
**Subject-months equals total observation time for all subjects in the period. Observation time for each subject equals time either until death or discontinuation of study medication.

Overall there were 59 patients who died on treatment in the Fragmin arm compared to 21 patients who died on treatment in the OAC arm. Also the total subject months (total observation time for all subjects in the period where observation time for each subject equals the time until death or discontinuation of study medication whichever came first) was 1402.68 for the Fragmin arm compared to 1286.90 in the OAC arm. The crude death rate for the on treatment group over the entire course of the study in the intention to treat population was higher in the Fragmin arm compared to the OAC arm (4.21 compared to 1.63, respectively). The number of patients that died in either study arm per month was highest in the first month (17/338 patients in the Fragmin arm compared to 11/335 patients in the OAC arm). There were 72/338 patients who died off treatment in the Fragmin arm compared to 116/338 patients who died off treatment in the OAC arm. In addition the crude death rate (number of subjects per total subject-months) for patients off treatment overall was slightly lower in the Fragmin arm compared to the OAC arm (10.92 compared to 14.31). The sponsor states that a change in anticoagulation therapy after discontinuation of study medication prior to death for the 6 month treatment period occurred in 157 patients in the Fragmin arm compared to 223 patients in the OAC arm as is shown in the table below.

Table 1.7 Change in Anticoagulation Therapies After Discontinuation of Study Medication Prior to Death: Six-Month Treatment Period

	Dalteparin (N=338)	OAC (N=338)
Deaths	131	137
During Treatment [1]	59	21
Off Treatment	72	116
Alternate Anticoagulation Therapies (pct) [2,3]		
None	74 (56.5)	64 (46.7)
LMWH	30 (22.9)	47 (34.3)
UFH	7 (5.3)	9 (6.6)
OAC	5 (3.8)	34 (24.8)
OTHER	41 (31.3)	69 (50.4)
Total Therapy Changes	157	223

1 Includes all deaths that occur within one day of study drug discontinuation
2 Patients may be included in more than one therapy category
3 Percentages are based on total deaths in category (numerator) and total deaths in period (denominator)

Taken as a whole it appears that some of the explanation for the difference in mortality rate between the two treatment arms for those patients who are on treatment may be due to the fact that patients were on treatment longer in the Fragmin arm than in the OAC arm and therefore more deaths occurred in the on treatment group treated with Fragmin arm compared to the on treatment group treated with OAC. Because this was an open label study, it would appear from the sponsor's table 1.7 (shown above) from the submission dated March 1, 2006, that investigators were less likely to proceed with alternate therapies for previously Fragmin treated patients compared to previously treated OAC patients. The sponsor states that patients that ultimately died during the "on-treatment" period and who were in the palliative, end-of life setting for their underlying cancer would potentially have their therapy managed differently. In this palliative setting investigator selection of anticoagulant therapy in the terminal phase of cancer may be biased by clinical factors such as vomiting, ability to swallow, daily monitoring dietary status and other factors. From the reviewer generated table above titled "On Treatment Solid Tumor Group that Died due to Underlying Malignancy", there were 34/50 patients that were on active therapy (either chemo or radiation) at the time of entry into the study in the Fragmin arm compared to 7/12 such patients in the OAC arm. There were 16/50 and 5/12 patients in the Fragmin and OAC arms, respectively, that were not undergoing any type of anticancer therapy at the time of entry into the study from the on treatment solid tumor group that died due to underlying cancer. However, the database provided does not allow further characterization of these patients with regard to those that were not initially on active anticancer treatment and subsequently stopped anti-cancer therapy or those that were not on active anticancer treatment initially and then went on anticancer treatment. Therefore, it is not possible to determine which patients may or may not be considered truly managed palliatively with

regard to their cancer treatment. Despite the fact that overall the mortality rate over the entire course of the study was essentially the same (see above figure entitled Time-to-Death Following Randomization – 12 month time period) and the fact that Fragmin administration is approved as a safe and effective means of VTE prophylaxis in the acute setting, there remains the problem of a higher treatment discontinuation rate of Fragmin due to morality compared to OAC. In this study of long term extended treatment of VTE, the discrepancy between the two treatment arms in terms of the mortality rate while on treatment cannot be explained by the number of fatal VTE events, fatal/major bleeding events or other high grade adverse events (as will be discussed below) that occurred to patients in the Fragmin arm of the CLOT study. Therefore, Fragmin should not be approved for the indication being sought.

B. In order to address the issue regarding the safety concern of possible liver toxicity with long-term exposure to Fragmin the sponsor was asked to provide an analysis of the transaminase level by Common Toxicity Criteria (CTC) grade and CTC grade ≥ 3 for liver enzymes and bilirubin. At the monthly time points starting from month 0 the sponsor was to include the number of patients at that time point. The curves were to be generated from the Fragmin safety database. Separate curves were to be generated for patients with chronic diseases and acute severe illnesses. Since the CLOT study included patients that had, most likely, the longest duration of exposure to Fragmin, the sponsor was to generate curves for that study population separately as well. This information request was communicated to the sponsor in the teleconference held on February 7, 2006. The sponsor submitted their response on February 17, 2006.

In addition the February 17, 2006 submission contained information regarding the potential for hepatic injury with long-term exposure to Fragmin. As was suspected, the sponsor has stated that there are no studies and the Fragmin database similar to the CLOT study in terms of high-dose long duration treatment with Fragmin. Sponsor provided Kaplan-Meier curves for the time to first elevation of aminotransferase (AST, ALT, ALP, and GGT) and total bilirubin at 6 months for CTC grades ≥ 3. The curves indicate that Fragmin treated patients had a slightly higher probability of elevated liver enzyme events and bilirubin over the course of treatment but the differences between the 2 treatment arms were not statistically significant. The table below indicates the number of events of elevation of liver enzymes with CTC grade ≥ 3 over 6 months.

Elevated Liver Function Events with CTC ≥ 3 over 6 months*

Liver enzyme	Fragmin n = 338	OAC n = 338
AST	8	3
ALT	12	7
ALP	11	7
GGT	19	19
Bilirubin	10	5

* Reviewer table generated from February 17, 2006 submission pages 13-17.

The data provided indicate that over a 6 month treatment period Fragmin may in a small proportion of people cause elevation in hepatic enzymes or bilirubin but this number was not significantly greater than that observed in patients treated with OAC. There may also be some influence of elevation of liver function indicators due to chemotherapy in both arms of the study. Over the course of the study the sponsor reported that the only grade 4 level in hepatic enzymes was observed in GGT and total bilirubin as is shown in the tables below.

T16.4 Incidence of Elevated Hepatic Enzymes: GGT

Dalteparin

Study Period	No. of Patients	NCI CTC Grade											
		0		1		2		3		4		>=3	
		n	%	n	%	n	%	n	%	n	%	n	%
Baseline	248	88	35.5	90	36.3	34	13.7	32	12.9	4	1.6	36	14.5
1 Week	204	45	22.1	81	39.7	45	22.1	25	12.3	8	3.9	33	16.2
1 Month	195	67	34.4	72	36.9	31	15.9	23	11.8	2	1.0	25	12.8
3 Month	151	68	45.0	44	29.1	25	16.6	11	7.3	3	2.0	14	9.3
6 Month	126	60	47.6	39	31.0	15	11.9	10	7.9	2	1.6	12	9.5

T16.4 Incidence of Elevated Hepatic Enzymes: GGT

OAC

Study Period	No. of Patients	NCI CTC Grade											
		0		1		2		3		4		>=3	
		n	%	n	%	n	%	n	%	n	%	n	%
Baseline	226	76	33.6	87	38.5	34	15.0	18	8.0	11	4.9	29	12.8
1 Week	173	46	26.6	68	39.3	27	15.6	21	12.1	11	6.4	32	18.5
1 Month	164	71	43.3	56	34.1	22	13.4	12	7.3	3	1.8	15	9.1
3 Month	120	68	56.7	38	31.7	8	6.7	6	5.0	0	0.0	6	5.0
6 Month	99	58	58.6	29	29.3	4	4.0	6	6.1	2	2.0	8	8.1

T16.5 Incidence of Elevated Hepatic Enzymes: Total Bilirubin

Dalteparin

Study Period	No. of Patients	NCI CTC Grade											
		0		1		2		3		4		>=3	
		n	%	n	%	n	%	n	%	n	%	n	%
Baseline	289	256	88.6	18	6.2	10	3.5	4	1.4	1	0.3	5	1.7
1 Week	240	217	90.4	7	2.9	8	3.3	5	2.1	3	1.3	8	3.3
1 Month	238	220	92.4	8	3.4	5	2.1	4	1.7	1	0.4	5	2.1
3 Month	183	173	94.5	6	3.3	3	1.6	0	0.0	1	0.5	1	0.5
6 Month	150	138	92.0	8	5.3	3	2.0	1	0.7	0	0.0	1	0.7

T16.5 Incidence of Elevated Hepatic Enzymes: Total Bilirubin

OAC

Study Period	No. of Patients	NCI CTC Grade											
		0		1		2		3		4		>=3	
		n	%	n	%	n	%	n	%	n	%	n	%
Baseline	266	237	89.1	18	6.8	4	1.5	6	2.3	1	0.4	7	2.6
1 Week	208	187	89.9	12	5.8	5	2.4	3	1.4	1	0.5	4	1.9
1 Month	207	192	92.8	6	2.9	6	2.9	2	1.0	1	0.5	3	1.4
3 Month	152	145	95.4	2	1.3	2	1.3	3	2.0	0	0.0	3	2.0
6 Month	120	113	94.2	5	4.2	2	1.7	0	0.0	0	0.0	0	0.0

The tables show that the number of patients with grade 4 elevations in GGT and total bilirubin were small and did not have a likely impact on the discrepancy in the mortality rate observed between the on treatment Fragmin group and the on treatment OAC group. Also, the tables indicate that by the first week of therapy with Fragmin some patients progressed to grade 4 elevations in GGT and total bilirubin. There were an additional 4 patients by week 1 that had a grade 4 level of GGT elevation compared to 0 additional patients in the OAC group that developed grade 4 elevations in GGT. Similarly, there were an additional 2 patients by week 1 that had a grade 4 level of total bilirubin in the Fragmin group compared to 0 additional patients in the OAC group that developed grade 4 elevations in total bilirubin. It does not appear that the number of patients with

grade 4 elevations in GGT and total bilirubin would have a significant impact on the rate of discontinuation of Fragmin due to death.

C. In the CLOT study there were 57/338, 17% of patients in the Fragmin arm compared to 43/335, 13% of patients in the OAC arm that had a platelet count <100,000/µl and ≥ 50,000/µl (moderate range thrombocytopenia). There were also 19/338, 6% of patients in the Fragmin arm and 10/335, 3% of patients that had a platelet count <50,000/µl (severe range thrombocytopenia). Furthermore, platelet count decrease was the reason for treatment modification or interruption in 27/338, 8% of patients in the Fragmin arm compared to 5/335, 2% of patients in the OAC arm. There were 217/338, 64% of patients in the Fragmin arm compared to 194/335, 58% of patients in the OAC arm that underwent concurrent chemotherapy which may have impacted on the thrombocytopenia results from the CLOT study. However in order to better understand the timing of the thrombocytopenia and to possibly better understand if thrombocytopenia may have impacted the mortality rate indirectly by decreasing the amount of chemotherapy that a patient would have been exposed to, the sponsor was asked to perform an additional analysis to show the time of onset of severe thrombocytopenia by week for the entire 6 month study period. In addition, the sponsor was asked to perform an analysis of the number of patients by treatment group who had moderate thrombocytopenia and severe thrombocytopenia from the time point of <1 month, ≥ 1 month to < 6 months and 6 months to 12 months. The sponsor was also to provide an analysis of the number of patients by treatment group for the number of chemotherapy cycles prior to platelets falling into the moderate range. These requests were communicated to the sponsor in the teleconference held on February 7, 2006.

The February 17, 2006 submission contained information regarding the incidence of thrombocytopenia as is shown in the table below.

Table T15.2 Incidence of Onset of Platelet Counts < 50,000/uL by Period (ITT Population)

Study Period (month)	Dalteparin (N=338)			OAC (N=338)		
	N	# of Subjects with Platelet Counts < 50,000/uL	%	N	# of Subjects with Platelet Counts < 50,000/uL	%
<1 month	338	11	3.25	338	5	1.48
>=1 month to < 6 months	302	10	3.31	301	4	1.33
>=6 months to <= 12 months	197	1	0.51	191	0	0.00
Total	338	22	6.51	338	9	2.66

The table shows that overall there were 22 patients with platelet counts < 50,000/µl in the Fragmin arm compared to 9 patients that developed platelet counts < 50,000/µl in the OAC arm. However, the sponsor states that in this group of patients with platelet counts < 50,000/µl, there were only 13 in the

Fragmin arm and 4 in the OAC arm that had interruptions due to platelet counts < 50,000/μl. This indicates that generally patients that should have had interruptions in treatment with Fragmin did not have interruptions. This may be due to the open label design of the study, ease of administration of study drug or physician comfort with the safety of the drug. The fact that fewer than the expected number of patients actually had interruptions indicates that indeed physicians may have been less likely to discontinue or change therapy with Fragmin even given the very ill nature of the majority of patients in this study. However, as was described previously, in the on treatment group with solid tumor malignancies who died, there was only a 1.4 fold increase in the number of days on treatment in the Fragmin group compared to a 4.2 fold increase in the number of deaths in the Fragmin treated patients with solid tumor malignancies.

D. In the approvable letter dated January 14, 2005, the sponsor was asked to consider further studies to investigate how best to transition patients from Fragmin to OAC should that change in therapy become necessary for a patient. The sponsor responded by stating that issues of what questions are clinically relevant for vitamin K antagonist OAC and who should undertake the design and implementation of studies to explore these questions are not issues that they feel they can address. In particular, the sponsor emphasizes that studies to explore the issues surrounding transition from Fragmin to OAC should be undertaken by the NDA holders for OAC or other parties that may wish to support specific research projects in this area. This response appears to be acceptable.

E. Additional concern is raised due to the fact that the use of Fragmin for this indication has been widely circulated in both peer reviewed and non-peer reviewed publications.[2] The sponsor should address this issue with a public statement that Fragmin is currently not indicated for the extended treatment and prophylaxis of VTE in patients with cancer.

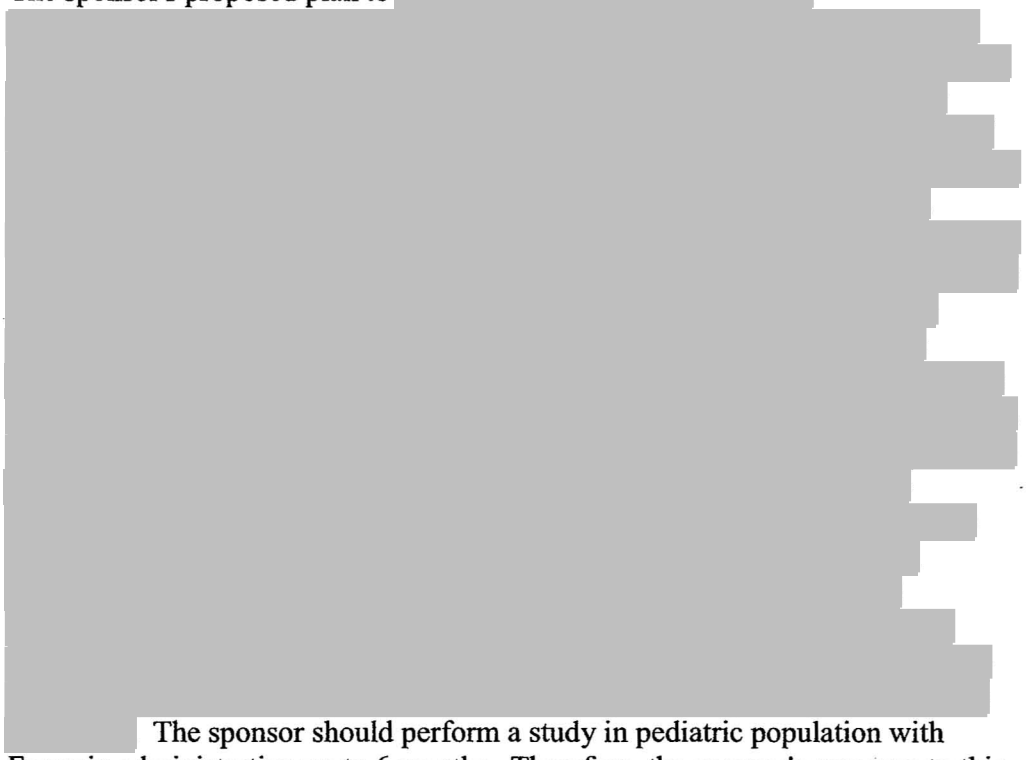
Therefore the indication being sought by the sponsor is not approvable primarily due to the fact that there was higher rate of discontinuation of Fragmin due to death in the Fragmin arm compared to the OAC arm in the CLOT study which could not be explained. Although a longer duration of treatment in the Fragmin arm may have allowed for more time for mortality events to occur, this does not fully explain the almost 4 fold higher rate of discontinuation of Fragmin due to mortality in the CLOT study. There remains the possibility that Fragmin itself may have impacted this mortality rate. The sponsor should perform a randomized double blind, double dummy study in order to evaluate the safety and efficacy of Fragmin for this indication.

III. Conclusions

The sponsor has submitted a response to the approvable letter dated January 14, 2005. In this current submission the sponsor addresses some of the main points of concern highlighted in that letter.

The sponsor's response to concerns regarding Fragmin extended use in cancer patients with renal impairment and in patients with hematologic malignancies is acceptable. The analysis presented by the sponsor indicates that renally impaired cancer patients treated with Fragmin had less recurrent VTE then OAC treated renally impaired cancer patients. The discrepancy between the two treatment arms in patients with hematologic malignancies with recurrent VTE can be explained by differences in subject baseline characteristics and underlying VTE risk factors. The sponsor has also acceptably responded to the issue regarding the transition of patients from Fragmin to OAC.

The sponsor's proposed plan to (b) (4)



The sponsor should perform a study in pediatric population with Fragmin administration up to 6 months. Therefore, the sponsor's response to this concern is not acceptable. The sponsor should propose a new pediatric plan which compares anti-factor Xa levels to VTE treatment efficacy and other clinical outcomes such as bleeding and possible liver toxicity. In addition, this new study in pediatric cancer patients should be limited to those patients with VTE and stratify the patients according to underlying presence or absence of a CVL.

In addition, this review has indicated that there are additional concerns which are nonetheless important for this indication and drug namely:

- The sponsor should address concerns regarding the higher rate of discontinuation due to death in the Fragmin arm compared to the OAC arm. However, overall there does not appear to be a difference in the rate

of mortality between the two treatment arms over the course of the study and at the 6 month and 12-month time points.

- The sponsor should alter the currently proposed study to evaluate Fragmin in the non-metastatic setting to be a randomized double blind, double dummy study. This is due to the fact that the open label design of the study may have had an impact on the rate of discontinuation of Fragmin due to mortality i.e., there were possibly more discontinuations due to death in the Fragmin arm because these patients were on treatment with Fragmin for a longer period of time.
- Therefore the submission for this indication is not approvable.

IV. Recommendations

The second cycle review has shown that the application for Fragmin for the extended treatment of symptomatic venous thromboembolism (VTE) i.e., either a proximal DVT and/or PE and to prevent recurrent VTE in patients with cancer is not approvable. The primary reason for the not approvable recommendation is the fact that there was an unexplained increased rate of discontinuation of Fragmin compared to OAC due to death.

Before the application may be approved the sponsor should address the following deficiencies:

- The sponsor should address concerns regarding the increased mortality rate in the CLOT study in the Fragmin arm while on treatment compared to the OAC arm while on treatment. The sponsor should perform another study which has a double blind, double dummy design with sufficient numbers of patients enrolled to determine the safety and efficacy of Fragmin for the indication being sought. Any studies performed in patients with non-metastatic malignancies for the current indication should be of similar design.
- In order to satisfy PREA requirements the sponsor should propose a new pediatric plan which compares anti-factor Xa levels to VTE treatment efficacy and other clinical outcomes such as bleeding and possible liver toxicity. In addition, this new study in pediatric cancer patients should be limited to those patients with VTE and stratify the patients according to underlying presence or absence of a CVL. The sponsor should submit a final protocol for review.

Additional concern is raised due to the fact that the use of Fragmin for this indication has been widely circulated in both peer reviewed and non-peer reviewed publications.[3] The sponsor should address this issue with a public statement that Fragmin is currently not indicated for the extended treatment and prophylaxis of VTE in patients with cancer.

Possible draft labeling is attached to this review for consideration if the sponsor conducts a successful additional study as recommended above. The Clinical

Trials section should also include results of the new study conducted for the indication.

28 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

References:

[1] Blom, J.W. et al.: Malignancies, prothrombotic mutations and the risk of venous thrombosis. JAMA. 2005. 293(6):715-722.
[2] Buller, H.R. et al.: Antithrombotic therapy for venous thromboembolic disease. Chest. 2004. 126(3): 401S-428S.
[3] Buller, H.R. et al.: Antithrombotic therapy for venous thromboembolic disease. Chest. 2004. 126(3): 401S-428S.

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/s/

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3/13/2006 01:48:46 PM
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3/13/2006 04:44:24 PM
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See also my Medical Team Leader secondary review memorandum dated 3/13/06.

CLINICAL REVIEW

Application Type	sNDA
Submission Number	20287
Submission Code	SE-035
Letter Date	March 16, 2004
Stamp Date	March 18, 2004
PDUFA Goal Date	January 17, 2005
Reviewer Name	Andrew Dmytrijuk, M.D.
Review Completion Date	January 14, 2005
Established Name	Dalteparin
(Proposed) Trade Name	Fragmin
Therapeutic Class	Anticoagulant
Applicant	Pfizer Inc. 235 East 42nd St. New York, NY 10017
Priority Designation	Standard
Formulation	Low Molecular Weight Heparin
Dosing Regimen	Subcutaneous
Indication	Extended treatment of symptomatic venous thromboembolism
Intended Population	Adult cancer patients

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ALT (SGPT)	Alanine aminotransferase (serum glutamate-pyruvate transaminase)
ACCP	American College of Chest Physicians
AST (SGOT)	Aspartate aminotransferase (serum glutamate-oxaloacetate transaminase)
aPTT	Activated partial thromboplastin time
Anti-FXa	Anti-Factor Xa activity
BID	Twice Daily
CAC	Central Adjudication Committee
CI	Confidence Interval
CTMG	Clinical Trials Methodology Group
CVT	Central venous thrombosis of the upper limb(s), neck, or chest
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
FRIC Study	Fragmin in Unstable Coronary Artery Disease Study
FRISC Study	Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease Study
F_{1+2}	Plasma prothrombin fragment 1+2
GGT	Gamma-glutamyl transpeptidase
HIT	Heparin-induced thrombocytopenia
INR	International Normalized Ratio
ITT	Intent-to-treat
IV	Intravenous
LMWH	Low molecular weight heparin
OAC	Oral anticoagulant
PE	Pulmonary embolism
PF4	Platelet factor 4
PT	Prothrombin time
qD	Once Daily
SAE	Serious adverse event
SC	Subcutaneous
TAT	Thrombin-antithrombin complex
TFPI	Tissue factor pathway inhibitor
TT	Thrombin time
UCAD	Unstable Coronary Artery Disease
UFH	Unfractionated heparin
USPI	United States Package Insert
VTE	Venous thromboembolism

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Dalteparin should be approved for the following indication:

- Extended treatment of symptomatic venous thromboembolism (VTE including, both deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) to prevent recurrent VTE in patients with cancer. The dose proposed is 200 IU/kg total body weight subcutaneously once daily for the first month followed by 150 IU/kg subcutaneously once daily for the next 5 months for a total of 6 months of treatment.

The rationale for this approval recommendation is based on the following information:

- The efficacy of the proposed therapy as supported by the CLOT study, which was a randomized, open-label, actively controlled, multicenter, multinational trial comparing a current standard of care, dalteparin initially with subsequent oral anticoagulation (OAC) to a novel regimen of dalteparin alone.
- The safety of this regimen was supported by information from the CLOT study and the overall weight of the safety record for dalteparin previously established.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

- Usual post-marketing monitoring and reporting.

1.2.2 Required Phase 4 Commitments

- A study of the effectiveness and safety of the use of dalteparin in patients with hematological tumors who have developed VTE.
- A study of the effectiveness and safety of the use of dalteparin in patients with non-metastatic tumors who have developed VTE.
- A study of the effectiveness and safety of the use of dalteparin in patients with cancer and renal dysfunction who have developed VTE
- A study of the effectiveness and safety of the use of dalteparin in pediatric patients with cancer who have developed VTE.

1.2.3 Other Phase 4 Requests

- None requested.

1.3 Summary of Clinical Findings

NDA 20287 is supported by the pivotal study identified by the protocol number 98-FRAG-069, also known as the CLOT (Randomized Comparison of Low Molecular Weight Heparin versus Oral Warfarin Therapy for Long Term Anticoagulation in Cancer Patients with Venous Thromboembolism) study. The CLOT study was a phase III, randomized, open-label, actively controlled, multicenter, multinational trial comparing dalteparin alone to dalteparin followed by OAC. The period of treatment was 180 days.

Dalteparin was first approved in Germany on August 26, 1985 as an anticoagulant for patients on hemodialysis. Dalteparin was approved in the USA on December 22, 1994 for thromboprophylaxis in abdominal surgery for patients at risk for thromboembolic complications. Subsequently dalteparin was approved for: DVT prophylaxis in patients undergoing hip replacement surgery (March 1999); prophylaxis of ischemic complications in unstable angina and non-Q wave myocardial infarction when concurrently administered with aspirin (May 1999); and DVT prophylaxis which may lead to PE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness (November 2003). Since it was first brought to market, an estimated (b) (4) patients have been prescribed dalteparin.

Post-Marketing safety surveillance was submitted in a report that covered the period from July 1, 1996 to November 29, 2001. A safety statement on adverse drug reactions was supplied and covers the period February 1, 2002 to May 1, 2003. Serious and non-serious adverse events are reported for the period covering May 1, 2003 to October 31, 2003. A safety update was also submitted for the period October 31, 2003 to July 17, 2004. A search of DSS revealed no other yearly reports, other than those listed here, that contained safety data. The above supplied post-marketing safety data indicate that there was no new safety information that alters the benefit/risk assessment of dalteparin for the already approved indications. The information that is provided reveals that the most frequently reported adverse reactions include hemorrhage, hematomas at the injection site, drug induced thrombocytopenia and elevation of liver transaminases. Skin necrosis, immunologically mediated thrombocytopenia leading to arterial and/or venous thrombosis or thromboembolism and allergic/anaphylactic reactions were also reported but only very rarely. These events are similar to those that would be expected for the LMWH class of drugs in terms of types and frequency of events.

1.3.1 Brief Overview of Clinical Program

Dalteparin is a low molecular weight heparin with anti-thrombotic activities. It acts by increasing the activity of anti-thrombin III which, in turn, decreases the activity of factor Xa. Inhibition of factor Xa retards the coagulation cascade and the formation of thrombin. Dalteparin is administered as a subcutaneous injection.

Dalteparin is currently indicated for:

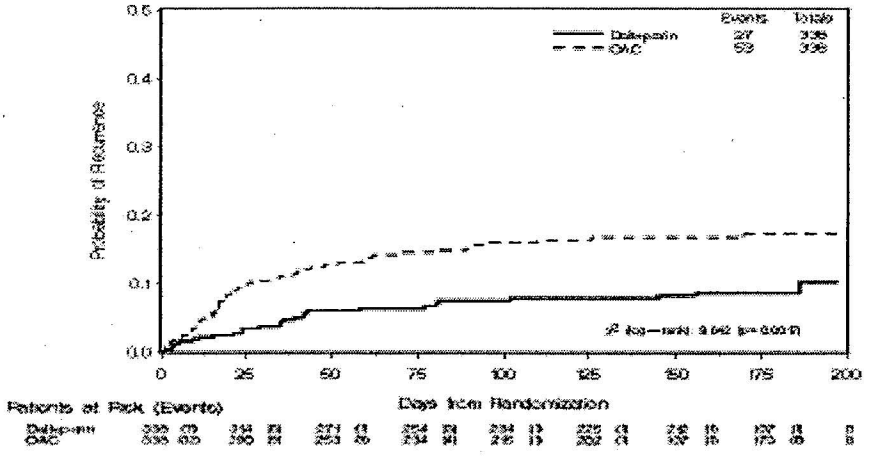
- Thromboprophylaxis in abdominal surgery for patients at risk for thrombotic complications.

- Prophylaxis of DVT in patients undergoing hip replacement surgery who are at risk for thromboembolic complications.
- Prophylaxis of ischemic complications in unstable angina and non-Q wave myocardial infarction when concurrently administered with aspirin therapy.
- Prophylaxis of DVT which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

1.3.2 Efficacy

The sponsor submitted a single trial (CLOT, 98-FRAG-069) in support of the indication. The main entry criteria for the study were age ≥ 16 years old, a diagnosis of a documented active malignancy (excluding basal cell or squamous cell carcinoma of the skin) and a current episode of an acute, symptomatic, objectively verified proximal lower limb DVT and/or PE. Patients were randomized in a 1:1 ratio to either the experimental or control arm. In the experimental (dalteparin) arm, patients received dalteparin, 200 IU/kg subcutaneously (s.c.) daily (qd) (maximum 18,000 IU) for 1 month, then dalteparin 150 IU/kg sc qd (maximum 18,000 IU) for an additional 5 months. In the active control arm (OAC), patients received dalteparin, 200 IU/kg sc qd (maximum 18,000 IU) for 5-7 days. This was overlapped with oral anticoagulation (OAC) (vitamin K antagonists) until the INR reached 2.0-3.0. Patients in this arm then completed a total of 6 months of therapy with OAC dosed to achieve a therapeutic INR of 2.0-3.0. Subjects were randomized and treated at 48 sites in North America, Europe, Australia and New Zealand. The primary outcome event was the recurrence of symptomatic VTE, defined as a symptomatic objectively documented DVT of the leg(s) or PE occurring during the 6 month study period as adjudicated by a Central Adjudication Committee (CAC). The VTE recurrence profile over time for each treatment group was described using Kaplan-Meier methodology and was compared using a two-sided log-rank test, allowing a type I error of 5% with the efficacy analysis set based on the intention to treat population. Secondary outcomes included clinically overt bleeding and death (overall mortality up to 6 months and 12 months post randomization). 676 patients were enrolled in the trial with an equal distribution in each arm. Baseline characteristics and prognostic factors were balanced between both arms. Most patients had solid tumors (90%) and stage IV disease (75%). The distribution of tumor types was comparable in the 2 arms of the study, with the most common primary histology being breast, gastrointestinal and lung. At entry, the qualifying VTE event in about 2/3 of patients was symptomatic proximal DVT only while 1/3 had both symptomatic proximal DVT and PE or PE alone. The duration of treatment was slightly longer in the dalteparin patients than in the OAC patients [median (range): 176 (1-205) days versus 167 (1-237) days, respectively]. Overall, 180 patients in the dalteparin arm and 163 patients in the OAC arm completed the full 6 months of treatment. A total of 27 (8.0%) dalteparin patients and 53 (15.7%) OAC patients experienced at least 1 adjudicated, symptomatic DVT and/or PE during the 6 month study period as shown in the figure below:

Figure 2. Time to First Recurrent Adjudicated-Positive VTE During the 6 Month Study Period - Kaplan-Meier Curves (ITT Population)



Source: Figure F5.1 of CLOT Clinical Study Report (Module 5.3.5.1).

Patients randomized to the dalteparin arm showed a 52% reduction in the recurrence of symptomatic VTE that was statistically significant (p=0.0016). The incidence of recurrent VTE was significantly less in the dalteparin arm (3.3%) versus (10.0%) OAC arm during the first 4 weeks of therapy suggesting a superior treatment effect of full dose dalteparin compared to dalteparin followed by OAC. There was little difference (5.2% vs. 7.0%, respectively) in recurrent VTE between the dalteparin and OAC arms during the period after 5 weeks.

Timing of Adjudicated VTEs (Intention to treat population)[1]

Study Period	Dalteparin 200 IU/kg (max. 18,000 IU) s.c. qd x 1 mo, then 150 IU/kg (max 18,000 IU) s.c. qd x 5 mo			OAC Fragmin 200 IU/kg (max 18,000 IU) s.c. qd x 5-7 d and OAC for 6 mo (target INR 2.0-3.0)		
	Number at Risk	Patients with VTE	%	Number at Risk	Patients with VTE	%
Week 1	338	5	1.5	338	8	2.4
Weeks 2-4	331	6	1.8	327	25	7.6
Weeks 5-28	307	16	5.2	284	20	7.0

[1]Three patients in the dalteparin group and 5 patients in the OAC group experienced more than 1 VTE over the 6 month study period. These patients were considered to have only 1 VTE.

The difference in treatment effect of dalteparin also remained statistically significant after the sponsor adjusted for factors found to be prognostic for outcome e.g., the type of qualifying thrombotic event at study entry (i.e., DVT or PE with or without DVT) as well as chronic (i.e., chronic immobilization, paralysis) or transient (i.e., surgery within the last 12 weeks, major trauma) risk factors.

The type of qualifying event at study entry (DVT or PE) was not predictive of a different risk of VTE recurrence over 6 months. Analysis of the composite secondary endpoint of symptomatic

lower limb first recurrent DVT, PE, or CVT [combined venous thromboembolism] at 6 months supports the findings from the analysis of the primary efficacy endpoint. There was no difference in the treatment arms with regard to the secondary endpoint of survival at 6 and 12 months. There did not appear to be a rebound effect after discontinuation of dalteparin therapy compared with OAC in the CLOT study.

1.3.3 Safety

The safety profile of dalteparin is reasonably well characterized. The sponsor states that an estimated (b) (4) patients worldwide have been prescribed dalteparin for a number of indications related to treatments or prophylaxis of VTE. The objective of the CLOT study was to address the poor outcomes experienced by many cancer patients with VTE by testing a new treatment regimen of dalteparin compared to a current standard of care, namely that of a LMWH combined with OAC. In the CLOT study the safety profile of dalteparin was comparable to the control arm in terms of overall frequency of adverse events (AE's), treatment discontinuations for drug-related adverse events, and frequency of serious adverse events (SAE's) including treatment related SAE's as seen in the table below.

Table 5. Overview of Frequency of Adverse Events and Serious Adverse Events – Any Relationship or Drug Related (Evaluable Population)

	Dalteparin N=337		OAC N=331	
	n	%	n	%
Patients with at least 1 AE	283	84.0	283	85.5
Patients with at least 1 study drug related AE	121	35.9	105	31.7
Patients with at least 1 serious adverse event	159	47.2	147	44.4
Patients with at least 1 study drug related serious adverse event	37	11.0	37	11.2

The evaluable population includes all patients in the as-treated population with available adverse event follow-up information.

Source: Table 19.1, Table 19.2, Table 19.4 and Table 19.6 of CLOT Clinical Study Report (Module 5.3.5.1).

Long term dalteparin treatment compared to OAC arm treatment was associated with a higher frequency of increased hepatic transaminases (11.2% vs.7.9%), ecchymoses (8.9% vs. 5.1%) and injection site reactions (11.6% vs. 3.0%). The frequency of ≥ grade 3 toxicity was low and rarely caused treatment discontinuation.

The frequency of major bleeding is shown in the table below.

Timing of Adjudicated Major Bleeding Events (As treated population)[1]

Study Period	Dalteparin 200 IU/kg (max. 18,000 IU) s.c. qd x 1 mo., then 150 IU/kg (max 18,000 IU) s.c. qd x 5 mo			OAC Fragmin 200 IU/kg (max 18,000 IU) s.c. qd x 5-7 d and OAC for 6 mo (target INR 2.0-3.0)		
	Number at Risk	Patients with Major Bleeding	%	Number at Risk	Patients with Major Bleeding	%
Week 1	338	4	1.2	335	4	1.2
Weeks 2-4	332	9	2.7	321	1	0.3
Weeks 5-26[2]	297	9	3.0	267	8	3.0

[1] Patients with multiple adjudicated major bleeding episodes within any time interval were counted only once in that interval. However, patients with multiple adjudicated major bleeding episodes that occurred at different time intervals were counted once in each interval in which the event occurred.
[2]Does not include one outlier in the OAC arm who received treatment for 33.9 weeks and had no VTE events.

A total of 22 and 13 major bleeding events occurred in the dalteparin and OAC arms respectively. The frequency of at least one major bleeding event was higher in the dalteparin arm (5.6%) than in the OAC arm (3.6%) (Fishers exact test, p=0.27). The majority of major bleeding episodes in the dalteparin arm occurred in the first month (13 of 22 episodes) when the higher dose of dalteparin was administered. There was a higher frequency of any bleeding observed in the OAC arm (18.5%) than in the dalteparin arm (13.6%) (Fishers exact test, p=0.09). Three patients in the dalteparin arm and 1 patient in the OAC arm experienced more than one major bleeding event during treatment. One patient in the OAC arm was treated for a period of 33.9 weeks.

Thrombocytopenia was reported as a treatment emergent adverse event in 37 (11%) of patients in the dalteparin arm and 27 (8.2%) of patients in the OAC arm. Thrombocytopenia that was considered to be directly related to dalteparin was reported in 15 (4.5%) of patients in the dalteparin arm and 7 (2.1%) of patients in the OAC arm.

Twenty seven of 338 (8.0%) patients in the dalteparin arm and 5 of 335 (1.5%) patients in the OAC arm had treatment modification or interruption due to decreased platelet counts. Two cases of antibody positive, heparin induced thrombocytopenia and 3 cases of drug related grade 3 (platelet counts < 50,000/mm^3) thrombocytopenia were reported in the dalteparin arm. These patients were also receiving chemotherapy with myelosuppressive potential at the time that these events occurred. Overall 12 serious adverse events for thrombocytopenia were reported in the dalteparin arm and 1 in the OAC arm.

Overall, a total of 190 of 338 (56.2%) dalteparin-treated patients and 194 of 335 (57.9%) OAC-treated patients died over the entire 12 month period. The majority of deaths in each treatment

arm occurred after the end of treatment (131 of 190 deaths in the dalteparin group and 173 of 194 deaths in the OAC group) and were judged related to underlying cancer.

1.3.4 Dosing Regimen and Administration

The dosing regimen employed by the sponsor was 200 IU/kg total body weight s.c. once daily (maximum 18,000 IU) for the first month followed by 150 IU/kg s.c. once daily (maximum 18,000 IU) for the next 5 months for a total of 6 months of treatment. The rationale for this regimen is based on previous studies performed by the sponsor. The dose is not currently approved for the indication in the U.S., but is approved in Canada and elsewhere for the initial treatment of acute VTE. The reduction in the dose of dalteparin after one month was based on the fact that there is a lower risk of recurrent VTE seen in the chronic treatment period.[1] In this study, dose reductions were also made for thrombocytopenia and renal dysfunction.

1.3.5 Drug-Drug Interactions

- Not applicable.

1.3.6 Special Populations

- Analysis of efficacy by age, gender and country favored the dalteparin arm. There were too few non-caucasians in the study to determine efficacy based on race. No pediatric patients were enrolled in the study.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Dalteparin (Fragmin) is a low molecular weight heparin (LMWH) with antithrombotic properties. Dalteparin, like other LMWH (such as enoxaparin and tinzaparin), has higher anti-Factor Xa (anti-FXa) activity and lower anti-factor IIa activity. Dalteparin binds to antithrombin III (ATIII) which potentiates the innate neutralization of FXa by ATIII, thereby interrupting the coagulation cascade and the formation of thrombin. Dalteparin has increased bioavailability and a prolonged half-life compared to UFH that allows once daily subcutaneous (SC) injection. Dalteparin is currently approved in the United States for the following indications:

- Thromboprophylaxis in abdominal surgery for patients at risk for thrombotic complications.
- Prophylaxis for DVT in patients undergoing hip replacement surgery who are at risk for thromboembolic complications.
- Prophylaxis of ischemic complications in unstable angina and non-Q wave myocardial infarction when concurrently administered with aspirin therapy.
- Prophylaxis of DVT which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

The sponsor wishes to add the following indication to the label:

- Extended treatment of symptomatic venous thromboembolism (VTE) i.e., either proximal deep venous thrombosis (DVT) and/or pulmonary embolism (PE)) and to prevent recurrent VTE in patients with cancer. The dose proposed is 200 IU/kg total body weight (maximum 18,000 IU) subcutaneously once daily for the first month followed by 150 IU/kg (maximum 18,000 IU) subcutaneously once daily for the next 5 months for a total of 6 months of treatment.

2.2 Currently Available Treatment for Indications

Currently available treatments for DVT and PE include: unfractionated heparin, other LMWHs such as enoxaparin, direct thrombin inhibitors such as argatroban and the vitamin K antagonist, warfarin. In the case of thromboprophylaxis a number of options are available which include warfarin, other LMWHs, the pentasaccharide fondaparinux, surgical intervention with inferior vena cava filter placement and compression stockings.

2.3 Availability of Proposed Active Ingredient in the United States

Dalteparin has been marketed since 1985. In the USA, dalteparin has been marketed since 1994. Dalteparin is also approved in over 60 countries worldwide. It has been prescribed to an estimated (b) (4) patients worldwide. The primary adverse event, as with all anticoagulants, is bleeding. Dalteparin labeling contains a black box warning for neuraxial hemorrhage with neurological deficits when the drug is used in patients who have had a lumbar puncture or epidural/spinal anesthesia.

2.4 Important Issues With Pharmacologically Related Products

Dalteparin and all other drugs of the LMWH class carry a black box warning that neuraxial anesthesia or spinal epidural puncture performed in patients anticoagulated or scheduled to be anticoagulated with LMWH or heparinoids for the prevention of VTE 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 with the use of indwelling epidural catheters for the administration of anesthesia or with the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs, platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture. The black box warning states that patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. In addition, the warning indicates that the physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

2.5 Presubmission Regulatory Activity

- Not applicable.

2.6 Other Relevant Background Information

- Not applicable.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

The statistical review indicates that the CLOT study demonstrated that dalteparin alone was superior to OAC in reducing the risk of recurrent symptomatic VTE in cancer patients. However, subgroup analysis of first recurrent adjudicated-positive VTE revealed that the superiority of dalteparin over OAC was somewhat inconsistent among subgroups of country, type of tumor (solid vs. hematological), extent of tumor, and history of previous VTE. The statistical reviewer further notes that survival between the 2 treatment arms was not statistically significantly different. The statistical reviewer believes that the efficacy shown in the CLOT study alone is not statistically persuasive and that these efficacy results have not been replicated in another study.

3.1 CMC (and Product Microbiology, if Applicable)

- No new information provided.

3.2 Animal Pharmacology/Toxicology

- No new information provided.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor submitted a single study in support of the application. The clinical information provided in this study includes data from one pivotal study identified by the protocol number 98-FRAG-069, also known as the CLOT study (Randomized Comparison of Low-Molecular Weight Heparin versus Oral Anticoagulation Therapy for Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism). Literature references provided by the sponsor are related to the pathophysiology, diagnosis and treatment of deep venous thrombosis along with discussions regarding the safety and efficacy of dalteparin in the treatment of thromboembolic disease. The sponsor also provided summaries of previous trials that support the efficacy and safety of dalteparin in the approved indications.

4.2 Tables of Clinical Studies

The Clot study was the only study reviewed to determine the safety and efficacy of dalteparin for this indication. Another study provided by the sponsor, the CATHETER trial (98-FRAG-076), which investigated the long term (16 weeks) use of dalteparin in the reduction of indwelling catheter thromboses was reviewed, but was deemed only peripherally supportive because of the differences in indication and doses of drug used.

4.3 Review Strategy

The medical review and a summary of the statistical review of the CLOT study is included in this document. An independent search of the literature was also performed for this review. Dalteparin has an established long term safety and efficacy profile in the setting of acute treatment and prophylaxis of VTE. Summaries of the studies submitted by the sponsor to support dalteparin's efficacy and safety in the treatment and prophylaxis of acute VTE in studies 86-96-291, 88-96-259, 88-96-297, 88-96-484, 89-96-060, 91-96-389, 91-96-544, 93-96-549, 94-96-235, 94-96-14, CATHETER 98-FRAG-076 were reviewed. In addition, summary results from studies CTN 91-128 (FRIC), TRN 91-115 (FRISC) and 95-FRAG-025 (FRISCII), which are trials to support the approved use of dalteparin in the setting of unstable coronary artery disease, were reviewed. Safety results in all studies were reviewed.

4.4 Data Quality and Integrity

On October 8, 2004, the Division of Scientific Investigations (DSI) was consulted to evaluate 1 study site, in London, Ontario, Canada based on insufficient domestic data and other adverse events at this site. The DSI audit concluded that there were minor good faith errors and that the data from this study could be used in support in the NDA supplement.

4.5 Compliance with Good Clinical Practices

The pivotal study supporting this sNDA and the supporting studies were conducted in accordance with accepted ethical standards and under the clinical practice guidelines. The informed consent for the CLOT study, protocol violations and site specific issues were reviewed and found to be within accepted standards. The CLOT study was conducted in compliance with the current revision of the Declaration of Helsinki, the ICH guidelines for Good Clinical Practices and applicable local regulatory requirements. The protocol and any amendments were approved by an IEC/IRB prior to initiation and continuation of the study. Written informed consent provided by the patient was required.

4.6 Financial Disclosures

The covered study (CLOT) was not funded via variable compensation and none of the investigators in the study held any form of proprietary interest in the product. The covered study was investigator-initiated by Professor Mark Levine and Dr. Agnes Lee, Hamilton Medical Centre, Ontario, Canada and sponsored by Pharmacia and Upjohn Inc., which provided dalteparin clinical supplies and clinical grants to support patient accrual and facilitate data sharing. The study was completed prior to the acquisition of Pharmacia by Pfizer. Pfizer has examined the significant payments of other sorts and equity information was provided by the investigators as defined in 21 CFR § 54.2. A total of 251 investigators are listed in the study. One of the listed investigators had financial information to disclose. On February 28, 2000 Dr. (b) (6) disclosed receiving a research grant of over $25,000 from Pharmacia. No investigators were listed as debarred.

5 CLINICAL PHARMACOLOGY

- No new data submitted.

5.1 Pharmacokinetics

- No new data submitted.

5.2 Pharmacodynamics

- No new data submitted.

5.3 Exposure-Response Relationships

- No new data submitted.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for dalteparin for this submission is: "For the extended treatment of symptomatic VTE (proximal DVT and/or PE) to prevent recurrent VTE in patients with cancer".

6.1.1 Methods

The clinical data upon which this application is submitted is based on a single study, (Study 98-FRAG-069, CLOT).

6.1.2 General Discussion of Endpoints

The primary endpoint was the first occurrence of symptomatic VTE (defined as lower limb DVT or PE or both) during the 6 month study period. Patients presenting with signs and symptoms of recurrent VTE were investigated according to prespecified diagnostic algorithms and diagnosed based on objective testing. Positive venography or compression ultrasound were accepted for the diagnosis of lower limb DVT. A suspected PE was confirmed on pulmonary angiography, V/Q scanning or V/Q scanning combined with compression ultrasonography (CUS) or venography, or on spiral CT.
The tables below list the criteria used during these tests.

Table 1. Criteria for Diagnosing Lower Limb DVT Post-baseline

Previous Venogram Available	Previous Venogram Unavailable
1. A new intraluminal filling defect in ≥2 projections on venography. 2. ≥5 cm extension of an intraluminal filling defect previously seen on a venograms	1. A constant intraluminal filling defect in ≥2 projections on venography. 2. Conversion of a previously fully compressible proximal venous segment on the most recent CUS to non-compressibility of that segment (venography was required for calf DVT found on CUS).

Source: Section 6.3.1.2.1 of CLOT Clinical Study Report (Module 5.3.5.1).

Table 2. Criteria for Diagnosing PE Post-baseline

Previous Pulmonary Angiogram Available	Previous Pulmonary Angiogram Unavailable
1. A new intraluminal filling defect on pulmonary angiography. 2. Extension of an existing defect on pulmonary angiography. 3. A new sudden cut-off of vessels >2.5 mm in diameter on a pulmonary angiogram.	1. An intraluminal filling defect on pulmonary angiography. 2. Sudden contrast cut-off of vessels >2.5 mm in diameter on a pulmonary angiogram. 3. A high probability V/Q scan which shows new or larger areas of segmental perfusion defects with ventilation mismatch in comparison to the baseline V/Q scan. 4. A non-high probability V/Q scan and satisfaction of the criteria for lower limb DVT. 5. A spiral CT scan showing new or unequivocal, unenhancing filling defect in the central pulmonary vasculature. 6. Evidence of PE at autopsy or a death within the 6 month study period that is attributable to PE.

Source: Section 6.5.1.2.1 of CLOT Clinical Study Report (Module 5.3.5.1).

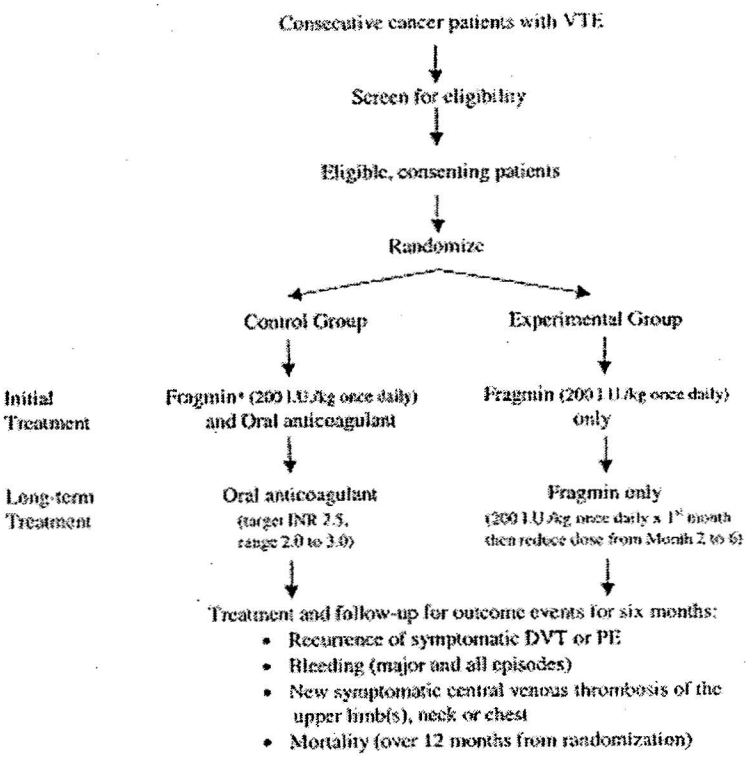
The secondary efficacy endpoints were as follows:

- First occurrence of a symptomatic and objectively documented lower limb DVT or PE or central venous thrombosis (CVT) during the 6 month study period.
- Survival at 6 and 12 months.

6.1.3 Study Design

- The CLOT study was an international, multicenter, open-label, active-control, randomized trial. There was a 1:1 randomization to the dalteparin arm vs. the dalteparin/OAC control arm at the time of a confirmed VTE diagnosis. The diagram below shows the basic study design.

18.1 Study Design



*In control group, Fragmin is continued for a minimum of five days and until the INR is therapeutic (target INR 2.5, range 2.0 to 3.0) for two consecutive days.

- The table below shows the schedule of assessment for this study.

Table 7. Schedule of Assessments

	Weeks																Months	
	R	1	2	4 1 mo	6	8	10	12 3 mos	14	16	18	20	22	24	26 6 mos	PD	9	12
Eligibility Assessment †	X																	
Baseline Assessment ††	X																	
Telephone Assessment ‡			X		X	X	X		X	X	X	X	X	X		X		
Clinical Assessment ‡‡		X		X				X							X			
Follow-up for mortality																	X	X
Adverse Event Assessment §		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Endpoint Assessment *		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CT = computerized tomography; γ-GT = gamma-glutamyl transpeptidase; INR = International Normalized Ratio; OAC = oral anticoagulant; PD = 30 days after permanent discontinuation of treatment; R = randomization

† Included: history and physical examination; patient's characteristics and prognostic factors; radiological investigations that could include compression ultrasound, contrast venography, spiral CT, ventilation-perfusion lung scan, pulmonary angiography

†† Included: bloodwork performed within 2 days prior to randomization or 24 hours after randomization, preferably before the first dose of study drug (complete blood count, platelets, ALT and/or AST, γ-GT, ALP, Na+, K+, Cl-, urea, creatinine, total bilirubin, albumin, INR, aPTT); and instruction to patients on self-administration of dalteparin and INR monitoring

‡ Requested information of signs/symptoms of primary/secondary endpoints; safety; concomitant medication; study drug and INR levels of OAC treated patients

‡‡ Included: history and physical examination; weight; bloodwork (same tests as at baseline); INR levels of OAC treated patients; study drug and drug dispensing if applicable

§ When study drug was discontinued before the 6-month period, AEs were assessed 30 days after last dose, and no longer assessed for the study period, with the exception of study drug-related AEs or SAEs that were to be followed until resolution or when they became stable or chronic.

* Assessment of signs/symptoms of primary/secondary endpoints and plan of investigations as per diagnostic algorithms if applicable

- 677 patients were randomized with 338 in the dalteparin arm and 339 in the OAC arm. One patient in the OAC arm did not have an informed consent and was excluded from the study before receiving treatment. Three other patients in the OAC arm did not receive any treatment. Therefore, the intention to treat population had 338 patients in the dalteparin arm and 338 patients in the OAC arm. The as-treated population had 338 in the dalteparin arm and 335 in the OAC arm. There were 180 patients vs. 163 patients that completed 6 months of treatment in the dalteparin arm and the OAC arm respectively in the as-treated population. There were 158 vs. 172 patients that discontinued treatment in the as-treated population in the dalteparin vs. OAC arms in this study. The inclusion and exclusion criteria for this study are listed below.

Patients potentially eligible for the study are consecutive in- or out-patients of either sex, who are age 16 years or older, with active malignancy, and are diagnosed with acute, symptomatic proximal lower limb DVT, PE or both, based on objective testing. Proximal lower limb DVT is defined as the presence of thrombus in the popliteal or more proximal veins.

Patients with active malignancy are those who meet any one of the following criteria at study entry:

1. Diagnosed with cancer within the past six months.
2. Have received any treatment (surgery, radiation, chemotherapy, hormonal therapy, palliative, or combined modality therapy) for cancer within the previous six months.
3. Currently receiving any treatment (surgery, radiation, chemotherapy, hormonal therapy, palliative, or combined modality therapy) for cancer.
4. Have documented recurrent or metastatic disease.

Patients with basal cell or squamous cell carcinoma of the skin are not considered to have active malignancy.

Patients are excluded from the study if they meet any one of the following criteria:

1. Body weight less than or equal to 40 kg.
2. Recurrent spontaneous fractures unrelated to the underlying active malignancy.
3. Administration of therapeutic doses of UFH or LMWH for more than 48 hours prior to randomization.
4. Need for long-term oral anticoagulant therapy (e.g., mechanical heart valves, atrial fibrillation).
5. Poor performance status with a score of 3 or 4 according to the Eastern Cooperative Oncology Group (ECOG) scale (33) (Appendix 18.3).
6. Serious hemorrhage requiring hospitalization, transfusion, or surgical intervention within two weeks of presentation.
7. Known acute (symptomatic or active bleeding) gastroduodenal ulcer.
8. Epidural/spinal puncture within the last 24 hours.
9. Neurosurgery within four weeks of presentation or any previous history of intracranial hemorrhage.
10. Septic endocarditis.
11. Overt pericardial effusion.
12. Current platelet count of less than 75 x 10^9/L.
13. Undergoing high dose chemotherapy for peripheral blood stem cell or bone marrow transplantation, induction chemotherapy for acute leukemia, or has other conditions associated with persistent thrombocytopenia of less than 100 x 10^9/L for a duration of ≥ four consecutive weeks.
14. Familial bleeding diathesis.
15. Uncontrolled hypertension despite antihypertensive therapy.
16. Dependent on renal dialysis or significant renal failure with a creatinine of greater than three times upper limit of normal control.
17. Allergy to anticoagulants (UFH, LMWH, or coumarin derivatives) including immune-mediated heparin-induced thrombocytopenia.
18. Allergy to contrast medium.
19. Pregnant or of childbearing potential and not using adequate contraception.
20. Geographically inaccessible for follow-up.
21. Failure to give written informed consent.

- Patients in the control group were to receive dalteparin 200 I.U./kg SC qd (max 18,000 IU) for 5-7 days overlapping with OAC until a goal INR of 2-3 was obtained and then continued on OAC with a target INR of 2-3 for a total of 6 months. Patients in the dalteparin only arm received dalteparin 200 IU/kg (max 18,000 IU) SC qd for 1 month and then a dose of 150 IU/kg (max 18,000 IU) SC qd for the remaining 5 months of treatment. Treatment continued until occurrence of VTE, the occurrence of an

unacceptable toxic/adverse event, physician or patient decision to discontinue therapy, or when the 6 month treatment was completed. Patients were followed for survival for an additional 6 months, up to 12 months after randomization. Patients were assessed at scheduled clinic visits at day 7-10, and ends of month 1, month 3 and month 6. At each clinic visit, blood samples were collected for hematology, hepatic and renal function studies. Coagulation parameters including INR and activated partial thromboplastin time were assessed. Patients were also contacted every 2 weeks by telephone. Patients were asked about any modification or interruption in study drug, missed doses and if any adjustment in the OAC had been made based on INR. Patients were asked about their general health and on signs and symptoms of VTE recurrence or central venous thrombosis (CVT), bleeding or other adverse events. If there was a suspected thrombosis, the patient underwent appropriate investigation according to pre-defined algorithms. The tables below show the criteria used in the CLOT study for diagnosing a lower limb VTE and PE respectively.

Table 3. Criteria for Diagnosing Lower Limb DVT during Follow-up

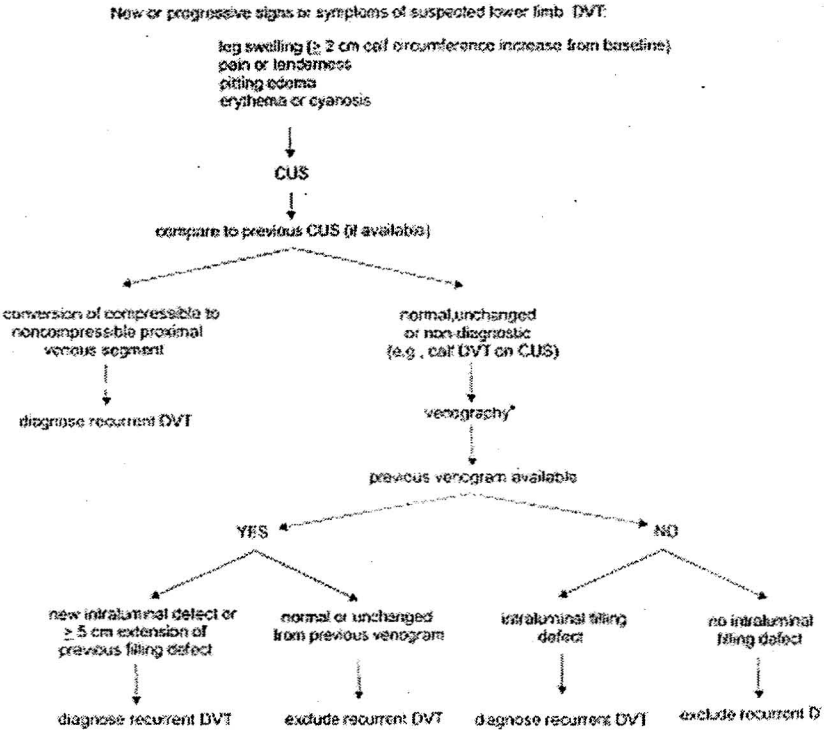
Previous venogram available	Previous venogram unavailable
1. A new intraluminal filling defect in two or more projections on venography.	1. A constant intraluminal filling defect in two or more projections on venography.
2. 5 cm or more extension of an intraluminal filling defect previously seen on a venogram.	2. Conversion of a previously fully compressible proximal venous segment on the most recent CUS to non-compressibility of that segment (venography is required for calf DVT found on CUS).

Table 4. Criteria for Diagnosing PE during Follow-up

Previous pulmonary angiogram available	Previous pulmonary angiogram unavailable
1. A new intraluminal filling defect on pulmonary angiography.	1. An intraluminal filling defect on pulmonary angiography.
2. Extension of an existing defect on pulmonary angiography.	2. Sudden contrast cut-off of vessels more than 2.5 mm in diameter on a pulmonary angiogram.
3. A new sudden cut-off of vessels more than 2.5 mm in diameter on a pulmonary angiogram.	3. A high probability VQ scan which shows new or larger areas of segmental perfusion defects with ventilation mismatch in comparison to the baseline VQ scan.
	4. A non-high probability VQ scan and satisfaction of the criteria for lower limb DVT.
	5. A spiral CT scan showing new or unequivocal, unenhancing filling defect in the central pulmonary vasculature (see section 7.3.2).
	6. Evidence of PE at autopsy or a death within the six-month study period that is attributable to PE.

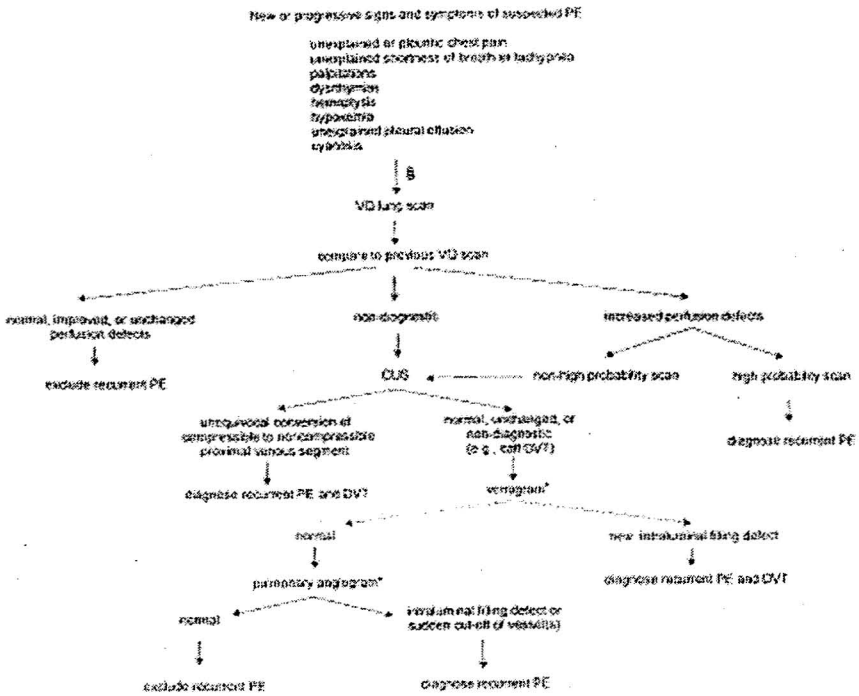
The diagrams below show the diagnostic algorithms used for patients with suspected DVT, PE and VTE of the upper limb(s), neck or chest respectively.

18.6 Diagnostic Algorithm for Patients with Clinically Suspected Lower Limb DVT



* If significant renal failure precludes investigations requiring contrast medium, then a positive result on serial CUS can be accepted as diagnostic of recurrent DVT.

18.7 Diagnostic Algorithm for Patients with Clinically Suspected PE

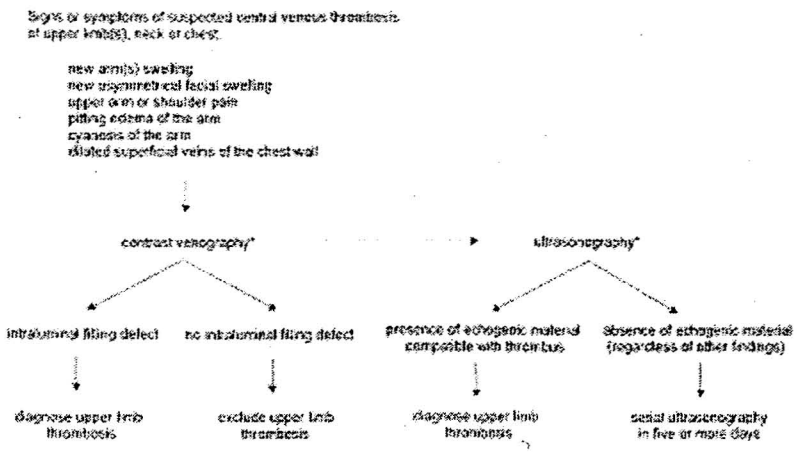


§ In centers where spiral CT is available, it may be performed prior to a VQ lung scan. An unequivocal, unenhancing filling defect in the central pulmonary vasculature may be considered as diagnostic for PE. All other results will be considered as non-diagnostic and further investigations will have to be performed as outlined in this algorithm.

* If significant renal failure precludes investigations requiring contrast medium, then a positive result on serial CUS can be accepted as diagnostic of recurrent DVT.

* For patients with a low clinical likelihood of PE, or who are unstable to undergo pulmonary angiography, a positive result on serial CUS may be accepted for diagnosis of recurrent PE and DVT.

18.8 Diagnostic Algorithm for Patients with Clinically Suspected Central Venous thrombosis of the Upper Limb(s), Neck or Chest



* Venography is the preferred diagnostic test. If renal failure or technical difficulties precludes performing venography, then ultrasonography may be performed. In the absence of echogenic material on the ultrasound, serial ultrasonography is required. If two serial ultrasounds 5 or more days apart do not show echogenic material, then upper limb thrombosis is considered excluded.

6.1.4 Efficacy Findings

Patients randomized to dalteparin alone received a median daily dose of 198 IU/kg during the first month of the study and a median daily dose of 162 IU/kg during the remaining study period. There were 2 types of OAC used. All except 2 countries used warfarin (about 90% of patients). Spain and the Netherlands used acenocoumarol (approximately 10% of patients). The mean treatment duration in the as-treated population in the dalteparin vs. OAC arms was 126.3 and 116.9 days respectively. The median treatment duration in the as-treated population in the dalteparin vs. OAC arms was 175.5 and 167.0 days (standard dev = 69.4 and 74.0 respectively). The minimum and maximum number of treatment days in the as-treated population in the dalteparin vs. OAC arms was 1.0 (min) in both arms and 205.0 and 237.0 (max) respectively. Patients in the OAC arm had a mean proportion of total treatment time with the INR in the therapeutic range (2.0-3.0) of 51.4%. The mean proportion of total treatment time with an INR >3.0 was 24.6% and the mean proportion of total treatment time with an INR <2.0 was 24.0%. The duration of treatment with dalteparin and OAC is shown in the table below.

Table 1. Duration of Treatment (As-treated)

Study Period (month)	Dalteparin N=338		OAC N=335	
	n	%	n	%
<= 1	338	100.0	335	100.0
1-2	286	84.6	262	78.2
2-3	238	70.4	226	67.5
3-4	217	64.2	192	57.3
4-5	207	61.2	180	53.7
5-6	192	56.8	173	51.6
6-7	110	32.5	98	29.3
>=7	---	---	1	0.3
Median Duration (Range), days	176 (1-205)		167 (1-237)	

Source: Table 13.1 and Table 13.2 of CLOT Clinical Study Report (Module 5.3.5.1).

Demographic characteristics were similar between the 2 treatment arms in this study. The median age was 64 years in both arms. The distribution of the sexes of the patients was also similar in both arms. The 2 treatment arms were also comparable with regard to tumor type, performance status and prior treatment in the last 6 weeks of before entry into the study. The majority of patients had solid tumors and the majority were metastatic (Stage IV).

Table 2. Patient Characteristics at Baseline: Demography (ITT Population)

	Dalteparin (N=338)		OAC (N=338)	
	n	%	n	%
Males	159	47.0	169	50.0
Females	179	53.0	169	50.0
Age < 65 years	182	53.8	182	53.8
Age ≥ 65 years	156	46.2	156	46.2
Median age/years (range)	64 (22-85)		64 (28-89)	
Median weight/kg (range)	74 (39-132)		73 (40-128)	

Source: Table T2.1, Table T2.2, Table T2.6, Table T2.8, Table T2.9, Table T2.10 and Table T2.13 of CLOT Clinical Study Report (Module 5.3.5.1).

Table 3. Baseline Disease Characteristics (ITT Population)

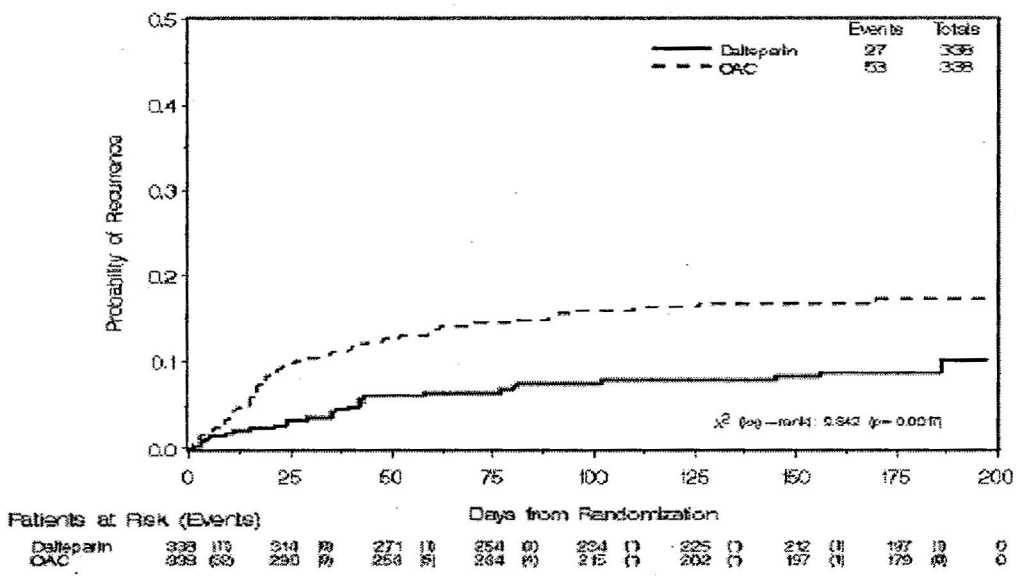
	Dalteparin (N=338)		OAC (N=338)	
	n	%	n	%
ECOG Performance status				
0	80	23.7	63	18.6
1	135	39.9	150	44.4
2	118	34.9	122	36.1
3	5	1.5	3	0.9
Tumor type				
Solid tumor	298	88.2	308	91.1
Gastrointestinal ‡	64	18.9	68	20.1
Breast	59	17.5	49	14.5
Lung	40	11.8	50	14.8
Prostate	25	7.4	22	6.5
Brain	14	4.1	13	3.8
Cervix	14	4.1	10	3.0
Pancreatic*	13	3.8	16	4.7
Uterus	13	3.8	2	0.6
Ovary	11	3.3	16	4.7
Bladder	10	3.0	19	5.6
Testicle	1	0.3	2	0.6
Other	33	9.8	42	12.4
Hematological tumor	40	11.8	30	8.9
Non-Hodgkin's lymphoma	22	6.5	15	4.4
Hodgkin's lymphoma	5	1.5	2	0.6
Leukemia	8	2.4	4	1.2
Multiple myeloma	4	1.2	8	2.4
Solid tumor status				
No evidence of tumor	36	(12.1) §	33	(10.7) §
Localized at primary site, no evidence of metastases	39	(13.1) §	43	(14.0) §
Metastatic	223	(74.8) §	232	(75.3) §
Hematological tumor status				
Not in Complete Remission	38	(95.0) ¶	29	(96.7) ¶
Complete Remission	2	(5.0) ¶	1	(3.3) ¶
Tumor treatment (last 6 weeks)				
Antineoplastic Treatment	217	64.2	194	57.4
Palliative Treatment	54	16.0	50	14.8
Radiotherapy	58	17.2	56	16.6
Surgery	37	10.9	50	14.8
None	55	16.3	64	18.9

Source: Table T2.1, Table T2.2, Table T2.6, Table T2.8, Table T2.9, Table T2.10, and Table T2.13 of CLOT Clinical Study Report (Module 5.3.5.1). ‡ Gastrointestinal tumors include: colorectal, colon, duodenum, rectal, esophageal, gastroesophageal, and gastric cancers. Figures in the table also include tumor types reported under "Other" tumor. * Also includes 1 dalteparin and 1 OAC patient reported under "Other". § Percentage was calculated versus the number of patients with solid tumors. ¶ Percentage was calculated versus the number of patients with hematologic tumors.

The primary comparison of the cumulative probability of the first VTE recurrence over the 6 month study period was statistically significant in favor of dalteparin (2 sided log-rank test, p=0.0017) and the estimated cumulative probability of recurrence at 6 months was reduced from

0.172 in the OAC arm to 0.087 in the dalteparin arm. The reduction of the VTE risk of recurrence over 6 months was 52 % in the dalteparin arm relative to the OAC arm (RR=0.48; 95%CI, 0.30-0.77; likelihood ratio test, p=0.0016). The graph below demonstrates this finding.

Figure 1. Time-to-First Recurrent Adjudicated-positive VTE During the 6 Month Study Period - Kaplan-Meier Curves (ITT Population)



Source: Figure F5.1 of CLOT Clinical Study Report (Module 5.3.5.1)

During the acute treatment period (Week 1) VTE recurrence was similar for the 2 treatments. The effect of dalteparin in decreasing the frequency of VTE was most marked during the first 4 weeks when the dose of dalteparin was 200 IU/kg daily in the dalteparin arm of the trial while the OAC arm was treated with oral anticoagulants. After the fourth week, at which time the dose of dalteparin was reduced to 150 IU/kg daily, there was no significant difference in the frequency of VTE in the 2 arms of the trial. The table below shows this comparison for the 2 groups.

Table 8. Timing of Adjudicated VTEs (ITT Population)

Study Period (weeks after randomization)	Dalteparin N=338 Pts at risk	Pts with VTE	%	OAC N=338 Pts at risk	Pts with VTE	%
Week 1 – acute VTE treatment	338	5	1.5	338	8	2.4
Week 2	334	2	0.6	330	8	2.4
Week 3	331	2	0.6	323	12	3.7
Week 4	327	2	0.6	315	5	1.6
Week 5	316	3	0.9	308	3	1.0
Week 6	305	4	1.3	299	3	1.0
Week 7	291	1	0.3	290	2	0.7
Week 8-11	285	3	1.1	282	6	2.1
Week 12-28	259	7	2.7	259	9	3.5

Source: Table T7.9 of CLOT Clinical Study Report (Module 5.3.5.1)

Overall the OAC arm patients were considered to have received adequate anticoagulation as the INR was >2.0 for an average 80% of the total treatment time. For the OAC treated patients, the mean proportion of total treatment time within, above and below the INR therapeutic range was 51.4%, 24.6% and 24.0% respectively. The distribution of the mean proportion of total treatment time above, below or within the INR therapeutic range did not differ between the OAC patients with and without a recurrent VTE.

There were 2 CVTs in the dalteparin group and 1 in the OAC group. The comparison of the cumulative probability of first DVT, PE or CVT recurrence over the 6 month study period was statistically significant and in favor of the dalteparin arm (two sided log-rank test, p=0.0028).

Table 10. Frequency of Adjudicated, Symptomatic Lower Limb DVT, PE, and CVT over 6 Months (ITT Population)

	Dalteparin N=338 N	%	OAC N=338 N	%
At least 1 event	29	8.6	54	16.0
Lower limb DVT	15	4.4	38	11.2
PE	10	3.0	11	3.3
Fatal PE	6	1.8	8	2.4
CVT	2	0.6	1	0.3

Source: Table T7.1 of CLOT Clinical Study Report (Module 5.3.5.1)

The survival between the 2 groups was not different and is shown in the table below.

Table 12. Kaplan-Meier Estimate for Time-to-Death at 6 and 12 Months (ITT Population)

		Event Occurred		Event Censored		Probability of Death	
	At Risk	N	%	N	%		95% CI
Analysis at 6 Months							
Dalteparin	338	131	38.8	207	61.2	0.390	(0.338, 0.442)
OAC	338	137	40.5	201	59.5	0.411	(0.358, 0.464)
Analysis at 12 Months							
Dalteparin	338	188	55.6	150	44.4	0.561	(0.508, 0.614)
OAC	338	192	56.8	146	43.2	0.580	(0.527, 0.634)

Source: Tables T7.11 and T7.12 of CLOT Clinical Study Report (Module 5.3.5.1).

The frequency and reasons for death were not different between the 2 groups and are shown in the table below. Most deaths were due to the underlying cancer. Six deaths in the dalteparin group and 8 deaths in the OAC group were adjudicated to be due to PE. Fatal bleeding was adjudicated in 3 and 1 patients in the dalteparin and OAC group respectively. A summary of deaths in the as-treated population is shown in the table below and in the table in section 7.1.1.

Table 14. Frequency of Adjudicated Deaths over 6 Months (ITT Population)

	Dalteparin N=338		OAC N=338	
	N	%	N	%
Total deaths at any time	131	100.0	137	100.0
Underlying cancer	119	90.8	124	90.5
Fatal PE	6	4.6	8	5.8
Fatal bleeding	3	2.3	1	0.7
Other cause	3	2.3	4	2.9

Source: Table T7.13 of CLOT Clinical Study Report (Module 5.3.5.1).

6.1.4 Clinical Microbiology

- Not applicable

6.1.5 Efficacy Conclusions

The analysis of the primary endpoint indicates that a course of 6 months of dalteparin treatment was superior to OAC in reducing the frequency of recurrent VTE in cancer patients. A total of 8.0% and 15.7% of patients in the dalteparin vs. OAC treated patients, respectively, experienced at least 1 adjudicated, symptomatic VTE during the 6 month study period. The primary comparison of the cumulative probability of the first VTE recurrence over the 6 month study period was statistically significant (two-sided log-rank test, p=0.0017) in favor of dalteparin. The estimated probability of recurrence at 6 months was reduced from 0.172 in the OAC group to 0.087 in the dalteparin group. A reduction of 52% in the frequency of VTE recurrence was

observed in the dalteparin group (risk ratio = 0.48 (95%CI 0.30, 0.77); p=0.0016) compared to the OAC group.

The results obtained for the as treated population and the results from the Cox model supported the findings of the primary analysis. The beneficial effect of dalteparin was greatest from the 2nd to 4th week of treatment and was maintained over the rest of the study period. The reduction in first recurrence of VTE was similar in patients receiving dalteparin whose qualifying event was DVT only and whose qualifying event was DVT or PE.

A total of 131 (38.8%) patients died during the 6 month study period in the dalteparin group and 137 (40.5%) in the OAC group. Over the total 12 month follow-up period, 188 (55.6%) and 192 (56.8%) died in each respective group. There was no significant difference between the 2 groups for mortality. Overall there was no significant difference in efficacy between the 2 treatment groups with regard to age or gender.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety parameters that were endpoints of the study included major bleeding events during the treatment period; any bleeding events during the treatment period; the type, incidence, severity, relatedness of adverse events; and abnormalities of hematology, coagulation and blood chemistry. Analyses were performed using the as-treated population, which included all patients who received study treatment. A bleeding event was defined as major if it was clinically overt and satisfied one of the following criteria: a decrease in hemoglobin of 2.0g/dl or more over a 24 hour period, bleeding leading to transfusion of two or more units of packed red cells, retroperitoneal, intracranial, intraspinal, intra-ocular, or pericardial bleeding documented by objective investigations and bleeding leading to death. In all the analyses concerning adverse events, the patient population consisted of all the treated patients with at least 1 available adverse event follow-up (337 patients in the dalteparin arm and 331 patients in the OAC arm).

During the study, 84.0% (283/337) of patients in the dalteparin arm and 85.5% (283/331) of patients in the OAC arm experienced one or more adverse events. The proportion of patients with at least 1 serious adverse event was similar in the 2 treatment arms (47.2% [159/337] in the dalteparin arm vs. 44.4% [147/331] in the OAC arm). The incidences of patients with drug related adverse events and drug related serious adverse events were also similar between the 2 treatment arms. The table below shows the overall frequency of patients reporting at least 1 treatment emergent adverse event both with and without any relationship to the drug.

Table 5. Overview of Frequency of Adverse Events and Serious Adverse Events – Any Relationship or Drug Related (Evaluable Population)

	Dalteparin N=337		OAC N=331	
	n	%	n	%
Patients with at least 1 AE	285	84.6	283	85.5
Patients with at least 1 study drug related AE	121	35.9	105	31.7
Patients with at least 1 serious adverse event	159	47.2	147	44.4
Patients with at least 1 study drug related serious adverse event	37	11.0	37	11.2

The evaluable population includes all patients in the as-treated population with available adverse event follow-up information.

Source: Table T9.1, Table T9.2, Table T9.4 and Table T9.6 of CLOT Clinical Study Report (Module 5.3.5.1).

Adverse events that were reported as common, i.e. >10% in the dalteparin arm were nausea, fatigue, decreased hemoglobin, increased gamma glutamyl transferase (GGT), vomiting, anorexia, increased alanine aminotransferase (ALT), injection site reaction and thrombocytopenia. Adverse events that were reported at >10% in the OAC arm were: fatigue, nausea, vomiting, dyspnea, constipation, diarrhea, increased GGT, decreased hemoglobin and anemia, abdominal pain and lower limb edema. There were no unexpected types of adverse events reported. The table below shows the frequency of treatment emergent adverse events that were reported in >5% of patients.

Table 6. Frequency of Treatment-emergent Adverse Events Reported in ≥5% of Patients by System Organ Class and Preferred Term - Any Drug Relationship, Any Grade and Worst CTC Grade by Patient (Evaluable Population)

System Organ Class	Preferred Term	Dalteparin N=337				OAC N=331			
		Any Grade		Grade ≥3		Any Grade		Grade ≥3	
		n	%	n	%	n	%	n	%
Blood and lymphatic system disorders	Anemia NOS	22	6.5	8	2.4	35	10.6	17	5.1
	Thrombocytopenia *	37	11.0	21	6.2	27	8.2	10	3.0
Cardiac disorders	Edema lower limb	26	7.7	1	0.3	34	10.3	4	1.2
Gastrointestinal disorders	Abdominal pain NOS	25	7.4	10	3.0	37	11.2	11	3.3
	Constipation	24	7.1	9	2.7	40	12.1	10	3.0
	Diarrhea NOS	30	8.9	6	1.8	39	11.8	6	1.8
	Nausea	72	21.4	10	3.0	58	17.5	11	3.3
	Vomiting NOS	46	13.6	11	3.3	53	16.0	17	5.1
General disorders and administration site conditions	Chest pain NEC	19	5.6	3	0.9	13	3.9	3	0.9
	Fatigue	54	16.0	12	3.6	62	18.7	17	5.1
	Injection site reaction †	39	11.6	2	0.6	10	3.0	1	0.3
	Pyrexia	25	7.4	5	1.5	32	9.7	6	1.8
	Weakness	20	5.9	5	1.5	17	5.1	7	2.1
Hepato-biliary disorders	Hypoproteinemia	26	7.7	6	1.8	29	8.8	6	1.8
Infections and infestations	Urinary tract infection NOS	19	5.6	8	2.4	21	6.3	4	1.2
Investigations	ALT increased	40	11.9	8	2.4	22	6.6	4	1.2
	AST increased	30	8.9	6	1.8	18	5.4	2	0.6
	Blood ALP NOS increased	28	8.3	9	2.7	26	7.9	7	2.1
	Blood creatinine increased	12	3.6	1	0.3	19	5.7	3	0.9
	Blood urea increased	14	4.2	0	0.0	23	6.9	1	0.3
	γ-GT increased	53	15.7	23	6.8	39	11.8	17	5.1
	Hemoglobin decreased	38	11.3	11	3.3	38	11.5	12	3.6
	INR increased	1	0.3	0	0.0	21	6.3	11	3.3
	Leukocyte count decreased	23	6.8	11	3.3	27	8.2	11	3.3
Metabolism and nutrition disorders	Anorexia	42	12.5	9	2.7	32	9.7	8	2.4
	Dehydration	21	6.2	14	4.2	14	4.2	10	3.0
	Hyponatremia	25	7.4	7	2.1	20	6.0	9	2.7
Musculoskeletal, connective tissue and bone disorders	Arthralgia	22	6.5	6	1.8	20	6.0	2	0.6
	Back pain	31	9.2	9	2.7	19	5.7	3	0.9
	Pain in limb	20	5.9	3	0.9	32	9.7	9	2.7
Neoplasm benign and malignant	Carcinoma NOS	25	7.4	22	6.5	15	4.5	12	3.6
Nervous system disorders	Headache NOS	19	5.6	1	0.3	13	3.9	1	0.3
Psychiatric disorders	Confusion	16	4.7	6	1.8	18	5.4	10	3.0
Respiratory, thoracic and mediastinal disorders	Cough	18	5.3	1	0.3	23	6.9	2	0.6
	Dyspnea NOS	33	9.8	18	5.3	45	13.6	21	6.3
	Pleural effusion	12	3.6	12	3.6	20	6.0	9	2.7
Skin & subcutaneous tissue disorders	Ecchymosis	30	8.9	0	0.0	17	5.1	0	0.0

Source: Table T9.1 of CLOT Clinical Study Report (Module 5.3.5.1). * Thrombocytopenia includes also the cases of "Platelet count decreased" reported in the SOC "Investigations", and the cases "Heparin-induced thrombocytopenia type II" reported in the SOC "General disorders and administration site conditions". † Injection site reaction includes also the cases of "Injection site bruising", "Injection site burning", "Injection site dermatitis", "Injection site erythema", "Injection site granuloma", "Injection site hemorrhage", "Injection site infection", "Injection site mass", "Injection site pain", and "Injection site reaction NOS".

The table below shows the frequency of treatment emergent adverse events that were reported as drug related.

Table 45. Frequency of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Drug Related, Worst CTC Grade by Patient (As-treated Population)

System Organ Class	Preferred Term	Dalteparin N=337				OAC N=331			
		Any Grade		Grade ≥3		Any Grade		Grade ≥3	
		N	%	N	%	N	%	N	%
At least one drug related adverse event		121	35.9	47	13.9	105	31.7	59	17.8
Blood and Lymphatic System Disorders	Any	22	6.5	15	4.5	15	4.5	9	2.7
	Anaemia NOS	5	1.5	2	0.6	11	3.3	7	2.1
	Thrombocytopenia *	15	4.5	9	2.7	7	2.1	3	0.9
Cardiac Disorders	Any	10	3.0	2	0.6	7	2.1	2	0.6
	Oedema NOS	3	0.9	1	0.3	4	1.2	1	0.3
	Oedema lower limb	5	1.5	0	0.0	3	0.9	1	0.3
Ear and Labyrinth Disorders	Any	1	0.3	1	0.3	2	0.6	1	0.3
Eye Disorders	Any	2	0.6	0	0.0	2	0.6	0	0.0
Gastrointestinal Disorders	Any	25	7.4	12	3.6	28	8.5	12	3.6
	Abdominal pain NOS	4	1.2	3	0.9	3	0.9	0	0.0
	Haematemesis	4	1.2	1	0.3	2	0.6	1	0.3
	Melena	4	1.2	2	0.6	6	1.8	2	0.6
	Nausea	8	2.4	3	0.9	4	1.2	0	0.0
	Vomiting NOS	2	0.6	0	0.0	8	2.4	3	0.9
General Disorders and Administration Site Conditions	Any	48	14.2	6	1.8	30	9.1	15	4.5
	Fatigue	8	2.4	3	0.9	12	3.6	7	2.1
	Haemorrhage NOS	4	1.2	1	0.3	5	1.5	4	1.2
	Injection site reaction †	34	10.1	1	0.3	5	1.5	0	0.0
	Pyrexia	3	0.9	1	0.3	4	1.2	0	0.0
Hepato-biliary Disorders	Any	5	1.5	1	0.3	8	2.4	2	0.6
	Hypoproteinemia	4	1.2	0	0.0	8	2.4	2	0.6
Immune System Disorders	Any	1	0.3	1	0.3	0	0.0	0	0.0
Infections and Infestations	Any	5	1.5	1	0.3	5	1.5	2	0.6
Injury and Poisoning	Any	4	1.2	0	0.0	4	1.2	3	0.9
Investigations	Any	38	11.3	19	5.6	48	14.5	27	8.2
	ALT increased	12	3.6	3	0.9	2	0.6	1	0.3
	AST increased	11	3.3	4	1.2	3	0.9	0	0.0
	Blood ALP NOS increased	9	2.7	3	0.9	4	1.2	0	0.0
	Blood creatinine increased	2	0.6	0	0.0	6	1.8	1	0.3
	Blood urea increased	2	0.6	0	0.0	6	1.8	0	0.0
	γ-GT increased	19	5.6	11	3.3	3	0.9	0	0.0
	Haematuria present	4	1.2	2	0.6	7	2.1	1	0.3
	Hemoglobin decreased	6	1.8	3	0.9	10	3.0	5	1.5
	INR decreased	0	0.0	0	0.0	6	1.8	5	1.5
	INR increased	0	0.0	0	0.0	18	5.4	10	3.0
	Leukocyte count decreased	3	0.9	1	0.3	4	1.2	2	0.6
	Prothrombin time prolonged	1	0.3	1	0.3	11	3.3	10	3.0
Metabolism and Nutrition Disorders	Any	9	2.7	6	1.8	11	3.3	5	1.5
	Anorexia	4	1.2	3	0.9	7	2.1	3	0.9
	Hyponatraemia	5	1.5	1	0.3	3	0.9	0	0.0
Musculoskeletal, Connective Tissue and Bone Disorders	Any	12	3.6	3	0.9	13	3.9	4	1.2

System Organ Class	Preferred Term	Dalteparin N=337				OAC N=331			
		Any Grade		Grade ≥3		Any Grade		Grade ≥3	
		N	%	N	%	N	%	N	%
	Arthralgia	2	0.6	0	0.0	4	1.2	1	0.3
	Pain in limb	2	0.6	0	0.0	7	2.1	1	0.3
Neoplasm Benign and Malignant	Any	6	1.8	6	1.8	5	1.5	5	1.5
Nervous System Disorders	Any	16	4.7	4	1.2	8	2.4	4	1.2
Psychiatric Disorders	Any	9	2.7	2	0.6	2	0.6	1	0.3
	Confusion	4	1.2	2	0.6	1	0.3	0	0.0
Renal and Urinary Disorders	Any	1	0.3	0	0.0	5	1.5	2	0.6
Reproductive System and Breast Disorders	Any	5	1.5	2	0.6	2	0.6	0	0.0
Respiratory, Thoracic and Mediastinal Disorders	Any	18	5.3	3	0.9	19	5.7	7	2.1
	Cough	2	0.6	0	0.0	4	1.2	0	0.0
	Dyspnea NOS	4	1.2	2	0.6	6	1.8	3	0.9
	Epistaxis	6	1.8	0	0.0	4	1.2	0	0.0
	Pleural effusion	1	0.3	1	0.3	5	1.5	1	0.3
Skin & subcutaneous tissue Disorders	Any	37	11.0	1	0.3	18	5.4	0	0.0
	Dermatitis NOS	4	1.2	0	0.0	4	1.2	0	0.0
	Ecchymosis	29	8.6	0	0.0	9	2.7	0	0.0
Vascular disorders	Any	9	2.7	3	0.9	11	3.3	6	1.8

Abbreviations: ALT =alanine aminotransferase; AST = aspartate aminotransferase; γ-GT = gamma-glutamyltransferase; OAC = oral anticoagulant

* Thrombocytopenia includes also the cases of "Platelet count decreased" reported in the SOC "Investigations", and the cases "Heparin-induced thrombocytopenia type II" reported in the SOC "General Disorders and Administration Site Conditions" (see Appendix 1.9 for documentation)

† Injection site reaction includes also the cases of "Injection site bruising", "Injection site burning", "Injection site dermatitis", "Injection site erythema", "Injection site granuloma", "Injection site hemorrhage", "Injection site infection", "Injection site mass", "Injection site pain", and "Injection site reaction NOS" (see Appendix 1.9 for documentation).

Source: Table T9.2

7.1.1 Deaths

Although the study period terminated at 6 months, patient survival was also determined at 12 months. All deaths that occurred over the 6 month study period were adjudicated by the central adjudication committee (CAC) and classified by cause into one of four categories: underlying cancer, fatal PE, fatal bleeding or other. Causes of death that occurred between 6 months and 12 months were not evaluated by the CAC but were based on the investigator's determination.

The majority of deaths in each treatment arm occurred after the end of treatment (131/190 deaths in the dalteparin arm vs. 173/194 deaths in the OAC arm. The majority of deaths were due to disease progression (90.8% in the dalteparin arm vs. 90.5% in the OAC arm). The frequency of death due to non-cancer related causes was similar between the 2 treatment arms (3.6% [12/338] in the dalteparin arm vs. 3.9% [13/335] in the OAC arm). Fatal PE was adjudicated as the cause of death in 6 dalteparin and 8 OAC treated patients. Two patients experienced fatal PE's after having a first recurrence of VTE and hence these fatal PE's were not included in the primary analysis. Fatal bleeding was the cause of death in 3 patients in the dalteparin group and 1 in the OAC group. Of the 3 patients in the dalteparin arm, 1 death from hemoptysis occurred during treatment in a lung cancer patient, while the other 2 deaths occurred after treatment discontinuation (1 died of cerebellar hemorrhage 20 days after treatment discontinuation and 1 died of gastrointestinal hemorrhage 81 days after treatment discontinuation). A colorectal cancer

patient died in the OAC group due to fatal bleeding (reported as melena) 5 days after treatment discontinuation. In the dalteparin arm the overall mortality rate was 56.2% (190/338 patients) compared to 57.9% (194/335 patients) in the OAC arm over the entire 12 month period.

More patients in the dalteparin arm (17.5% [59/338]) died during treatment compared to the OAC arm (6.3% [21/335]). The main reason for this difference is that more patients in the OAC arm had discontinued OAC because of a VTE event. Underlying cancer was the most common reason for on-treatment deaths (91.5% [54/59] in the dalteparin arm vs. 66.7% [14/21] in the OAC arm). The frequency of deaths due to non-cancer related reasons was comparable between the 2 treatment arms (1.5% [5/338] of patients in the dalteparin arm vs. 2.1% [7/335] of patients in the OAC arm). PE was fatal in 4 patients in the dalteparin group and 5 patients in the OAC group during treatment. Bleeding was adjudicated as the cause of death in 1 patient in the dalteparin arm during treatment. The table below summarizes the deaths in the as treated population.

Table 8. Summary of Deaths (As-treated Population)

Primary Cause of Death	Dalteparin N=338						OAC N=335					
	On Treatment		Off treatment		Total		On Treatment		Off treatment		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Total	59	17.5	131	38.8	190	56.2	21	6.3	173	51.6	194	57.9
Patients with adjudicated cause of death (first 6 months)												
All	59	17.5	72	21.3	131	38.8	21	6.3	116	34.6	137	40.9
Underlying cancer	54	16.0	65	19.2	119	35.2	14	4.2	110	32.8	124	37.0
Fatal PE	4	1.2	2	0.6	6	1.8	5	1.5	3	0.9	8	2.4
Fatal bleed	1	0.3	2	0.6	3	0.9	0	0.0	1	0.3	1	0.3
Other	0	0.0	3	0.9	3	0.9	2	0.6	2	0.6	4	1.2
Patients without adjudicated cause of death (from 6 to 12 months)												
All	...	...	59	17.5	59	17.5	...	...	57	17.0	57	17.0
Underlying cancer	...	...	45	13.3	45	13.3	...	...	45	13.4	45	13.4
Infection	...	...	5	1.5	5	1.5	...	...	3	0.9	3	0.9
Cardiac disorders	...	...	3	0.9	3	0.9	...	...	0	0.0	0	0.0
Renal disorders	...	...	3	0.9	3	0.9	...	...	1	0.3	1	0.3
Respiratory disorders	...	...	1	0.3	1	0.3	...	...	1	0.3	1	0.3
Bleed	...	...	0	0.0	0	0.0	...	...	1	0.3	1	0.3
Other	...	...	1	0.3	1	0.3	...	...	3	0.9	3	0.9
Unknown	...	...	1	0.3	1	0.3	...	...	3	0.9	3	0.9

Source: Tables T7.13, Table T9.7 and Appendix 3.6.3 of CLOT Clinical Study Report (Module 5.3.5.1).

7.1.2 Other Serious Adverse Events

In the dalteparin arm, 5.6% (19/338) of patients had at least 1 adjudicated major bleeding event compared to 3.6% (12/335) in the OAC arm (Fishers exact test, p=0.27). Only 1 fatal bleed occurred during treatment. This patient (701-004) had lung cancer and experienced severe hemoptysis after approximately 2 months of dalteparin treatment. Bleeding into clinically critical sites occurred in 1.2% of patients in the dalteparin group and in 0.9% in the OAC group. Ten patients (2.9%) in the dalteparin group and 5 (1.5%) in the OAC group permanently discontinued treatment due to major hemorrhagic events (see section 7.1.3).

The table below shows the timing of adjudicated major bleeding events. In the first week and from week 5 onward the major bleeding rate between the 2 treatment arms was similar. However, during weeks 2-4, during which time patients in the dalteparin arm continued on 200 IU/kg/d while patients in the OAC arm received oral anticoagulants only, the risk of major

bleeding was higher in the dalteparin arm (2.7% [9/332 patients at risk]) compared to the OAC arm (0.3% [1/321 patients at risk]).

Timing of Adjudicated Major Bleeding Events (As treated population)

Study Period	Dalteparin 200 IU/kg (max. 18,000 IU) s.c. qd x 1 mo., then 150 IU/kg (max 18,000 IU) s.c. qd x 5 mo			OAC Fragmin 200 IU/kg (max 18,000 IU) s.c. qd x 5-7 d and OAC for 6 mo (target INR 2.0-3.0)		
	Number at Risk	Patients with Major Bleeding	%	Number at Risk	Patients with Major Bleeding	%
Week 1	338	4	1.2	335	4	1.2
Weeks 2-4	332	9	2.7	321	1	0.3
Weeks 5-35	297	9	3.0	267	8	3.0

Note: patients with multiple adjudicated major bleeding episodes within any time interval were counted only once in that interval. However, patients with multiple adjudicated major bleeding episodes that occurred at different time intervals were counted once in each interval that the event occurred. A total of 22 and 13 major bleeding events occurred in the dalteparin and OAC arms respectively. Three patients in the dalteparin arm and 1 patient in the OAC arm experienced more than one major bleeding event during treatment. Also, 1 patient in the OAC arm was treated for a period of 237 days.

The analysis of any bleeding event was obtained by combining major and minor bleeding events. In the dalteparin arm, any bleeding occurred in 13.6% of patients compared to any bleeding in 18.5% of patients in the OAC arm (Fishers exact test, p=0.09). In both groups most of the bleeding was considered to be minor as shown in the table below.

Table 15. Frequency of Any Adjudicated Bleeding Event During Treatment (As-treated Population)

	Dalteparin N=338		OAC N=335	
	n	%	n	%
At least one bleeding event	46	13.6	62	18.5
Minor bleeding	30	8.9	50	14.9
Major Bleeding	19	5.6	12	3.6

Source: Table T8.1 of CLOT Clinical Study Report (Module 5.3.5.1).

7.1.3 Dropouts and Other Significant Adverse Events

The table below lists the 15 patients that permanently discontinued drug due to a major hemorrhagic event.

Table 12. Details of Patients Permanently Discontinued Due to a Major Hemorrhagic Event

Treatment group/ Patient	Age (years)	Sex	Detail of major hemorrhagic event
Dalteparin			
102-076	77	Female	Patient had experienced dizziness and pain in right thigh to calf, and increasing ecchymosis on Day 32. The event was associated with a decrease in hemoglobin, and a blood transfusion of 2 units was given. The event led to the permanent discontinuation of study medication.
110-001	46	Male	Patient had experienced shortness of breath on Day 7. The event was associated with ECG changes, a paradoxical pulse, an increased jugular venous pulse, and was confirmed on pericardiocentesis. The event led to the discontinuation of study medication.
212-011	65	Female	Patient had experienced profuse vaginal bleeding on Day 11. The patient's hemoglobin level had decreased, and she was transfused with 1 unit of packed red blood cells. The event led to permanent discontinuation.
215-016	56	Female	Patient had hematuria on Day 46 and the event led to the permanent discontinuation of study medication.
223-011	39	Female	Patient had vaginal bleeding, hematuria and a painful abdomen on Day 10. The event was associated with a decrease in hemoglobin, and thrombocytopenia (platelet count 28000/µL). A blood transfusion of 2 units was given. The event led to the permanent discontinuation of study medication.
303-001	50	Female	Patient had experienced nausea and vomiting, melena and hematemesis on Day 2. Mild confusion, a fall at home, anxiety and tremor in both arms were also noted. The patient's hemoglobin level had decreased and she received a blood transfusion of ≥ 2 units of packed red blood cells. The event led to permanent discontinuation.
504-016	73	Male	Patient had experienced hematemesis and melena on Day 10. The event was associated with decreased hemoglobin levels, and a blood transfusion of ≥2 units was given. The event led to the permanent discontinuation of study medication.
506-006	53	Male	Patient had a generalized seizure on Day 29. The patient had a history of epilepsy and glioblastoma multiforme. An MRI scan revealed a small hemorrhage anterior to the tumor. The event led to permanent discontinuation.
701-004	78	Male	Patient experienced massive hemoptysis on Day 71. The patient died as a result of the event.
702-003	47	Female	Patient experienced bleeding in the mouth, abdominal hematoma, fever (>38.4 °C) and petechiae on the right arm on Day 53. She received a blood transfusion of ≥ 2 units.
OAC			
206-004	59	Female	Patient was hospitalized after experiencing a gastrointestinal bleed on Day 64. The patient had low hemoglobin levels, INR levels of 4.6, and was found to have metastatic erosion of bladder. The patient received a blood transfusion of ≥ 2 units. Palliative bowel surgery and IVC filter insertion were planned. The event led to permanent discontinuation.
216-001	85	Male	Patient had experienced blood in the urine on Day 21. On arrival to hospital, hematuria was noted. Colonoscopy, and esophageal and duodenal gastroscopies were performed, and the patient received ≥ 2 units of blood. The event led to permanent discontinuation.
501-018	52	Female	Patient experienced an intra-abdominal hemorrhage on Day 7. The event was associated with a decrease in hemoglobin and thrombocytopenia (platelet count 99000/µL). A blood transfusion was given. The event led to permanent discontinuation.
504-009	81	Male	Patient had experienced headache, lethargy, incontinence, and hemorrhagic stroke on Day 120, and had scored 10-15 on the Glasgow coma scale. A Computed Tomography (CT) scan was performed indicating intracranial hemorrhage. The event led to permanent discontinuation.
706-001	53	Female	Patient had experienced gastric bleeding on Day 88 due to tumor growth in the stomach. The patient received a blood transfusion of ≥ 2 units. The event led to permanent discontinuation.

Source: Appendices 3.7.1 and 3.7.3 of CLOT Clinical Study Report (Module 5.3.5.1).

There was 1 patient in the dalteparin arm and 6 patients in the OAC arm that were discontinued from the study based on a contraindication to anticoagulation listed as "other". The "other" reasons for the discontinuation of these patients from the study are thrombocytopenia with platelet counts less than 50,000/mm^3 for the patient in the dalteparin arm. In the OAC arm, the "other" reasons for discontinuation were invasive procedures (2 patients), elevated INR (2 patients), biweekly paracentesis (1 patient) and increased risk of intracranial hemorrhage (1 patient). The 4 patients listed below as having been discontinued in the dalteparin arm due to abnormal blood work were all due to low platelet counts. However, the patient in the dalteparin arm who was discontinued for "other" reasons and described above was not included in the number of patients whose discontinuance was due to thrombocytopenia. Other reasons for discontinuation of treatment are shown in the table below.

Table 12. Reasons for Discontinuation (As-treated Population)

	Dalteparin N=338		OAC N=335		Total N=673	
	N	%	N	%	N	%
Patients who completed treatment	180	53.3	163	48.7	343	51.0
Patients who discontinued	158	46.7	172	51.3	330	49.0
Death	56	16.6	24	7.2	80	11.9
Underlying cancer	52	15.4	17	5.1	69	10.3
Fatal PE	3	0.9	5	1.5	8	1.2
Fatal bleeding	1	0.3	0	0.0	1	0.1
Other	0	0.0	2	0.6	2	0.3
Confirmed acute VTE	21	6.2	47	14.0	68	10.1
DVT	12	3.6	35	10.4	47	7.0
PE	7	2.1	10	3.0	17	2.5
CVT of upper limb	2	0.6	2	0.6	4	0.6
Contraindication to anticoagulation	12	3.6	25	7.5	37	5.5
Bleeding	10	3.0	19	5.7	29	4.3
Other	1	0.3	6	1.8	7	1.0
Missing	1	0.3	0	0.0	1	0.1
Adverse event	17	5.0	19	5.7	36	5.3
Abnormal bloodwork	4	1.2	4	1.2	8	1.2
Abnormal investigation results	1	0.3	1	0.3	2	0.3
Patient decision / withdrawal of consent	20	5.9	14	4.2	34	5.1
Other	27	8.0	38	11.3	65	9.7
Underlying cancer	17	5.0	21	6.3	38	5.6
Investigator decision	1	0.3	5	1.5	6	0.7
Patient unable to swallow	0	0.0	4	1.2	4	0.6

Abbreviations: CVT = central venous thrombosis; DVT = deep vein thrombosis; OAC = oral anticoagulant; PE = pulmonary embolism; VTE = venous thromboembolic event
Source: Table T1.4, Appendix 3.1.1, 3.1.2, and 3.6.3

7.1.4 Other Search Strategies

Review of adverse events regarding dalteparin from AERS reveals no new adverse events from those previously described. Most of the AE's are related to hemorrhage or thrombotic failure.

Post marketing surveillance (PSUR) data were provided by the sponsor as follows:

- PSUR July 1, 1996 to September 19, 1999.
- PSUR September 20, 1999 to November 29, 2001.

- Safety statement on suspect adverse drug reactions from February 1, 2002 to May 1, 2003.
- Line listing of serious and non-serious adverse events May 1, 2003 to October 31, 2003.
- Safety update from October 31, 2003 to July 17, 2004.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Patients were assessed while hospitalized and at scheduled clinic visits at day 7-10, month 1 (30 days), month 3, and month 6. Patients were also contacted every 2 weeks by telephone. Patients were questioned about their general health focusing on signs and symptoms of VTE recurrence or central venous thrombosis, bleeding episodes or other adverse events. In the case of suspected thrombosis, appropriate investigations were to be carried out, according to pre-defined diagnostic algorithms.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse events were characterized according to National Cancer Institute-Common Toxicity Criteria.

7.1.5.3 Incidence of common adverse events

Adverse events reported at an incidence of > 10% in the dalteparin group were: nausea, fatigue, decreased hemoglobin, increased gamma glutamyl transferase (GGT), vomiting, anorexia, increased alanine aminotransferase (ALT), injection site reaction, and thrombocytopenia. Adverse events reported at an incidence of >10% in the OAC group were: fatigue, nausea, vomiting, dyspnea, constipation, diarrhea, increased GGT, decreased hemoglobin and anemia, abdominal pain and lower limb edema. The profile of adverse events was as would be expected for the patient population studied and was consistent with the existing core data information for dalteparin.

7.1.5.4 Common adverse event tables

Table 6. Frequency of Treatment-emergent Adverse Events Reported in ≥5% of Patients by System Organ Class and Preferred Term - Any Drug Relationship, Any Grade and Worst CTC Grade by Patient (Evaluable Population)

System Organ Class	Preferred Term	Dalteparin N=337				OAC N=331			
		Any Grade		Grade ≥3		Any Grade		Grade ≥3	
		n	%	n	%	n	%	n	%
Blood and lymphatic system disorders	Anemia NOS	22	6.5	8	2.4	35	10.6	17	5.1
	Thrombocytopenia *	37	11.0	21	6.2	27	8.2	10	3.0
Cardiac disorders	Edema lower limb	26	7.7	1	0.3	34	10.3	4	1.2
Gastrointestinal disorders	Abdominal pain NOS	25	7.4	10	3.0	37	11.2	11	3.3
	Constipation	24	7.1	9	2.7	40	12.1	10	3.0
	Diarrhea NOS	30	8.9	6	1.8	39	11.8	6	1.8
	Nausea	72	21.4	10	3.0	58	17.5	11	3.3
	Vomiting NOS	46	13.6	11	3.3	53	16.0	17	5.1
General disorders and administration site conditions	Chest pain NEC	19	5.6	3	0.9	13	3.9	3	0.9
	Fatigue	54	16.0	12	3.6	62	18.7	17	5.1
	Injection site reaction †	39	11.6	2	0.6	10	3.0	1	0.3
	Pyrexia	25	7.4	5	1.5	32	9.7	6	1.8
	Weakness	20	5.9	5	1.5	17	5.1	7	2.1
Hepato-biliary disorders	Hypoproteinemia	26	7.7	6	1.8	29	8.8	6	1.8
Infections and infestations	Urinary tract infection NOS	19	5.6	8	2.4	21	6.3	4	1.2
Investigations	ALT increased	40	11.9	8	2.4	22	6.6	4	1.2
	AST increased	30	8.9	6	1.8	18	5.4	2	0.6
	Blood ALP NOS increased	28	8.3	9	2.7	26	7.9	7	2.1
	Blood creatinine increased	12	3.6	1	0.3	19	5.7	3	0.9
	Blood urea increased	14	4.2	0	0.0	23	6.9	1	0.3
	γ-GT increased	53	15.7	23	6.8	39	11.8	17	5.1
	Hemoglobin decreased	38	11.3	11	3.3	38	11.5	12	3.6
	INR increased	1	0.3	0	0.0	21	6.3	11	3.3
	Leukocyte count decreased	23	6.8	11	3.3	27	8.2	11	3.3
Metabolism and nutrition disorders	Anorexia	42	12.5	9	2.7	32	9.7	8	2.4
	Dehydration	21	6.2	14	4.2	14	4.2	10	3.0
	Hyponatremia	25	7.4	7	2.1	20	6.0	9	2.7
Musculoskeletal, connective tissue and bone disorders	Arthralgia	22	6.5	6	1.8	20	6.0	2	0.6
	Back pain	31	9.2	9	2.7	19	5.7	3	0.9
	Pain in limb	20	5.9	3	0.9	32	9.7	9	2.7
Neoplasm benign and malignant	Carcinoma NOS	25	7.4	22	6.5	15	4.5	12	3.6
Nervous system disorders	Headache NOS	19	5.6	1	0.3	13	3.9	1	0.3
Psychiatric disorders	Confusion	16	4.7	6	1.8	18	5.4	10	3.0
Respiratory, thoracic and mediastinal disorders	Cough	18	5.3	1	0.3	23	6.9	2	0.6
	Dyspnea NOS	33	9.8	18	5.3	45	13.6	21	6.3
	Pleural effusion	12	3.6	12	3.6	20	6.0	9	2.7
Skin & subcutaneous tissue disorders	Ecchymosis	30	8.9	0	0.0	17	5.1	0	0.0

Source: Table T9.1 of CLOT Clinical Study Report (Module 5.3.5.1). * Thrombocytopenia includes also the cases of "Platelet count decreased" reported in the SOC "Investigations", and the cases "Heparin-induced thrombocytopenia type II" reported in the SOC "General disorders and administration site conditions". † Injection site reaction includes also the cases of "Injection site bruising", "Injection site burning", "Injection site dermatitis", "Injection site erythema", "Injection site granuloma", "Injection site hemorrhage", "Injection site infection", "Injection site mass", "Injection site pain", and "Injection site reaction NOS".

7.1.5.5 Identifying common and drug-related adverse events

- Drug related adverse events are summarized in the table in section 7.1.5.4 by system organ class and severity. The profile of drug related adverse events was similar for the dalteparin and OAC groups. In each treatment group, events affecting the system organ classes general disorders and gastrointestinal disorders were the most frequently reported. Skin and subcutaneous tissue disorders were the only system organ class to show a notable difference between treatment groups (11% in the dalteparin group and 5.4% in the OAC group); this was mostly due to ecchymosis.

7.1.5.6 Additional analyses and explorations

- As discussed above, no differences in the type or frequency of adverse events could be determined from the data provided.

7.1.6 Less Common Adverse Events

- No data provided.

7.1.7 Laboratory Findings

No major differences in laboratory findings were observed between the 2 treatment arms.

7.1.7.1 Overview of laboratory testing in the development program

- The sponsor provided hematology, chemistry and coagulation parameters.

- Overall, 11.0% (37 patients) in the dalteparin arm and 8.2% (27 patients) in the OAC arm developed thrombocytopenia (platelet count < 100,000/mm^3) during the trial. Most of these patients were also receiving chemotherapy at the time these events were recorded. Thrombocytopenia believed to be related to study drug was reported in 4.5% (15) of patients in the dalteparin arm and 2.1% (7) of patients in the OAC arm. Three patients randomized to dalteparin developed heparin induced thrombocytopenia. These patients were also receiving chemotherapy at the time these events were recorded. The table below describes the frequency of thrombocytopenia.

Frequency of the Development of Thrombocytopenia (Platelet count < 100,000/mm^3)

	Dalteparin 200 IU/kg (max 18,000 IU) s.c. qd x 1 mo., then 150 IU/kg (max 18,000 IU) s.c. qd x 5mo.		OAC Fragmin 200 IU/kg (max 18,000 IU) s.c. qd x 5-7 d and OAC for 6 mo. (target INR 2.0-3.0)	
	N = 337		N = 331	
	N	%	N	%
Total Number of Thrombocytopenia	37	11	27	8.2
Drug Related Thrombocytopenia	15	4.5	7	2.1
Thrombocytopenia associated with HIT	3	0.9	0	0.0

- A decrease in platelet count was the reason for modification or interruption of treatment in 8.0% (27 of 338) patients in the dalteparin arm and 1.5% (5 of 335) patients in the OAC arm.

- Overall, changes in hemoglobin, platelet and white blood cell counts were similar in both treatment arms in the majority of patients. A decrease in hemoglobin was seen in 27.5% of patients in the dalteparin arm and 29.0% in the OAC arm. Severe cases of anemia were reported in 4.7% of patients in the dalteparin arm and 7.5% in the OAC arm. Thrombocytopenia and leucopenia were reported in less than 20% of patients.

Table 22. Frequency of Patients whose Hematological Findings Worsened in Severity versus Baseline [Any Grade (1 to 4) and Grade 3 to 4] (As-treated Population)

Laboratory Parameter	Dalteparin N=338				OAC N=335			
	Any Grade (≥1)		Grade 3-4		Any Grade (≥1)		Grade 3-4	
	n	%	n	%	n	%	n	%
Hemoglobin	93	27.5	16	4.7	97	29.0	25	7.5
Platelet Count	57	16.9	19	5.6	43	12.8	10	3.0
White Blood Cells	60	17.8	31	9.2	57	17.0	21	6.3
Worst CTC grade by patient								

Source: Table T10.1 of CLOT Clinical Study Report (Module 5.3.5.1)

- Treatment emergent aPTT abnormalities (> 2x upper limit of normal) were observed in more OAC than dalteparin treated patients (50.4% vs. 30.8% respectively). Values for INR increased as soon as the OAC treatment was started. INRs were not affected by dalteparin treatment. The mean INR over the course of the study for the OAC arm was 1.2 at baseline (n = 335; SD = 0.7), 2.8 at week 1 (n = 258; SD = 1.7), 2.5 at month 1 (n = 218; SD = 1.1), 2.5 at month 3 (n = 157; SD = 1.2) and 2.4 at month 6 (n = 128; SD = 1.1).

- Dalteparin treatment was associated with more frequent elevations of ALT, AST, GGT compared to OAC (39.9% vs. 31.0%, 34.3% vs. 28.4%, 41.1% vs. 31.3% of patients respectively). Severe abnormalities (≥ Grade 3 = >5-20.0x ULN) in ALT were seen in 4.1% of dalteparin treated vs. 2.1% of OAC treated patients and AST was severely abnormal in 3.0% of dalteparin treated patients vs. 0.9% of OAC treated patients. The percent of patients with ≥ Grade 3 GGT abnormalities was similar in the 2 treatment arms. In terms of alkaline phosphatase and bilirubin, abnormally high values were recorded in a similar proportion of patients in the 2 treatment groups. The table below shows the frequency of patients whose liver function tests worsened in severity. All the severe abnormalities of ALT and AST were of grade 3 on both treatments. Severe abnormalities of GGT were similarly frequent on both treatments (11.8% dalteparin patients and 9.9% OAC patients), as well as the grade 4 cases (12 dalteparin patients and 9 OAC patients). Treatment emergent abnormally high values of ALP (24.6% dalteparin patients and 23.3% OAC patients) and bilirubin (12.7% dalteparin and 11.3% OAC patients) were recorded in a similar proportion of patients in the 2 treatment groups. Severe abnormalities of ALP were recorded in 3.8% dalteparin patients and 3.9% OAC

patients while slightly more patients with ≥ grade 3 (> 3-10x ULN) bilirubin were observed in patients receiving dalteparin (3.6%) compared to patients receiving OAC (2.1%).

Table 25. Frequency of Patients whose Hepatic Enzyme and Bilirubin Findings Worsened in Severity versus Baseline (Any Grade [1 to 4] and Grade 3 to 4) (As-treated Population)

Laboratory Parameter	Dalteparin N=338				OAC N=335			
	Any Grade (≥1)		Grade 3-4		Any Grade (≥1)		Grade 3-4	
	n	%	n	%	n	%	n	%
ALT	135	39.9	14	4.1	104	31.0	7	2.1
AST	116	34.3	10	3.0	95	28.4	3	0.9
ALP	83	24.6	13	3.8	78	23.3	13	3.9
GGT	139	41.1	40	11.8	105	31.3	33	9.9
Total bilirubin	43	12.7	12	3.6	38	11.3	7	2.1

Worst CTC grade by patient
Source: Table T10.3 of CLOT Clinical Study Report (Module 5.3.5.1).

- Overall, creatinine values did not change as compared to baseline in the majority of patients on both treatments. Abnormalities in creatinine occurred at a similar frequency in both treatment arms (18.3% of patients in the dalteparin arm [n = 62] vs. 16.7% of OAC treated patients [n = 56]). Similar percentages of patients in both treatment arms showed abnormalities of ≥ grade 3 (> 3.0-6.0x ULN) (1.2% in the dalteparin arm and 2.1% in the OAC arm). The table below shows the frequency of treatment emergent creatinine abnormalities.

Table 57. Frequency of Treatment-Emergent Creatinine Abnormalities - Worst CTC Grade by Patient (As-treated Population)

	Dalteparin N=338				OAC N=335			
	Any Grade ≥1		Grade 3-4		Any Grade ≥1		Grade 3-4	
	N	%	N	%	N	%	N	%
Creatinine	62	18.3	4	1.2	56	16.7	7	2.1
	N		%		N		%	
Worse	62		18.3		56		16.7	
No change	243		71.9		227		67.8	
Better	8		2.4		9		2.7	

Abbreviations: OAC = oral anticoagulant
Source: Table T10.3

- Mean percent variations of electrolyte values as compared to baseline were comparable in the 2 treatment arms.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

- Not applicable.

7.1.7.3 Standard analyses and explorations of laboratory data

- Not applicable.

7.1.7.4 Additional analyses and explorations

- Not applicable.

7.1.7.5 Special assessments

- Not applicable.

7.1.8 Vital Signs

- No vital signs data were collected during the study.

7.1.9 Electrocardiograms (ECGs)

- This study did not evaluate for potential changes in EKG's during or after treatment.

7.1.10 Immunogenicity

- No immunogenicity data was collected during this study.

7.1.11 Human Carcinogenicity

- No carcinogenicity data was collected during this study.

7.1.12 Special Safety Studies

- No special studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

- Not applicable.

7.1.14 Human Reproduction and Pregnancy Data

- Pregnant patients and those of child bearing potential were excluded from the study. No pregnancies were reported during this study. Therefore, no data was submitted.

7.1.15 Assessment of Effect on Growth

- Not applicable.

7.1.16 Overdose Experience

During the study some patients received higher than planned doses of dalteparin. Dalteparin was to be dosed based on the patient's weight and as per protocol, the highest dose allowed was 18,000 IU/day. Overall, 8 patients in the dalteparin group and 6 patients in the OAC group who were receiving dalteparin in the initial period of VTE treatment (week 1) were documented to have received overdoses of dalteparin.

The overdoses of dalteparin received ranged from 23,400 IU/day to 100,000 IU/day. Approximately half of the patients receiving an overdose received only a one-time dalteparin overdose, usually during the initial treatment period, when patients were supplied with multi-dose vials of the drug. The clinical course of the patients receiving overdoses was unremarkable except for 1 patient who experienced a major bleeding event while the patient was receiving concomitant OAC therapy and had a supra-therapeutic INR (6.9).

7.1.17 Postmarketing Experience

Post-marketing experience safety surveillance was submitted in a report that covered the period from July 1, 1996 to November 29, 2001. A safety statement on adverse drug reactions was supplied and covers the period from February 1, 2002 to May 1, 2003. Serious and non-serious adverse events were reported for the period covering May 1, 2003 to October 31, 2003. A search of DSS revealed no other yearly reports that contained safety data. The above supplied post-marketing safety data indicate that there was no new safety information that alters the risk benefit assessment of dalteparin for the already approved indications. The information provided indicates that the most frequently reported adverse reactions include hemorrhage, hematomas at the injection site, drug induced thrombocytopenia and elevation of liver transaminases. Skin necrosis, immunologically mediated thrombocytopenia leading to arterial and/or venous thrombosis or thromboembolism, allergic/anaphylactic reactions were also reported but only very rarely. For example, during the period from September 20, 1999 to November 29, 2001 the total number of adverse events with regard to body system was 669. Of the total number of adverse events, bleeding comprised approximately 22%, thrombocytopenia comprised approximately 13%, and hematomas comprised approximately 5%. The remainder of the adverse events comprised approximately 1% or less of the total number of adverse events by body system reported for this time period. These events are similar to those that would be expected for this class of LMWH drugs in terms of types and frequency of events.

7.2 Adequacy of Patient Exposure and Safety Assessments

The study was adequately designed to permit an evaluation for both efficacy and safety in the described population.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Dalteparin has been evaluated in a number of different studies to support the previously noted approved indications. In addition, dalteparin has been prescribed to over (b) (4) times. The safety experience with dalteparin is extensive and no new safety concerns were raised in this study.

Narratives of adverse events are provided by the sponsor for the following categories:

- Deaths occurring on treatment and within 30 days after treatment discontinuation for reasons unrelated to cancer.
- Serious adverse events deemed related to dalteparin.

7.2.1.1 Study type and design/patient enumeration

- The design of this study and selection of this population is appropriate for the indication sought by the sponsor.

7.2.1.2 Demographics

- The demographic characteristics of the patients in the study were similar between the 2 treatment arms. The median age was 64 years in both groups and the distribution of males and females was balanced in both arms. The 2 groups were generally comparable with regard to tumor type, performance status and prior treatment in the last 6 weeks. The majority of patients had a solid tumor and most were metastatic. Although the study was not powered to determine differences in the degree of thrombogenesis of any one particular malignancy, more patients randomized to the OAC arm appeared to have had a thrombogenic tumor (lung, GI) while more dalteparin randomized patients had a less thrombogenic tumor (breast). The 2 groups were comparable with regard to qualifying VTE and previous VTE. For almost 70% of patients, the qualifying episode of VTE was DVT only. The 2 groups were comparable with regard to risk factors for VTE. Within 12 weeks prior to randomization, approximately 25% of patients in each group had been hospitalized or confined to bed for at least 3 days and approximately 20% had major surgery. More than 50% of patients in each group were current or former smokers and approximately 40% of patients consumed alcohol. At study entry, less than 20% of patients in each group were receiving anti-platelet agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin. During the 6 month study period about 30% of patients in each group received concomitant anti-platelet agents (mainly NSAIDs). There were no notable differences between the treatment groups in the use of prior or concomitant medications. The demographics of the patients included in the CLOT study are shown in the tables in section 6.1.4.

7.2.1.3 Extent of exposure (dose/duration)

Patients randomized to dalteparin received a median daily dose of 198 IU/kg during the first month and a median daily dose of 162 IU/kg during the remaining study period. Two types of OAC were used: all except 2 countries used warfarin (approximately 90% of patients) while 2 European countries used acenocoumarol (approximately 10% of patients). For patients in the OAC group the mean proportion of total treatment time with the INR in the target range (2.0-3.0) was 51.4%. The mean proportion of total treatment time with INR>3.0 was 24.6% and the mean proportion of total treatment time with an INR <2.0 was 24.0%.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

As noted previously, dalteparin has an extensive established safety and efficacy record. The CLOT study was primarily used to support the claim of safety and efficacy for this indication. Postmarketing Experience is described in section 7.1.17.

7.2.2.1 Other studies

- Previous dalteparin studies submitted did not primarily include patients with malignancy. The CATHETER study, although including patients with malignancy, included patients that had thromboses related to a mechanical (foreign device) inserted into the venous system and thus it does not directly correlate to either safety or efficacy in this CLOT study. Additionally, the dose of dalteparin in the CATHETER study (5000 U SC qd) was much lower than the dose given in the CLOT study.

7.2.2.2 Postmarketing experience

- See section 7.1.17.

7.2.2.3 Literature

- Current literature supports the use of 6 months of LMWH treatment in patients with cancer who have had a DVT. The 7th ACCP (American College of Chest Physicians) Conference on Antithrombotic and Thrombolytic Therapy supports this use as a Grade 1A recommendation (experts are very certain that benefits do outweigh the risks, burdens and costs and that this is based on consistent results from randomized clinical trials), "for most patients with DVT and cancer, we recommend treatment with LMWH for at least 3 to 6 months of long term treatment". The authors further note that, "The regimens of LMWH that have been established to be effective for long term treatment in randomized trials are dalteparin 200 IU/kg body weight [SC] qd for 1 month, followed by 150 IU/kg body weight [SC] qd thereafter or tinzaparin, 175 IU/kg body weight SC qd".[3,4] This 1A for dalteparin recommendation is based on the CLOT study.

7.2.3 Adequacy of Overall Clinical Experience

The study was carried out in a randomized controlled fashion for a period of 6 months allowing adequate analysis of the clinical experience. Patients were followed for an additional 6 months for mortality. This allowed for adequate long term safety and survival data to be acquired with this regimen.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

- Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

The CLOT study analyzed the appropriate endpoints and safety data.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

- Not applicable.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor's evaluation of the potential adverse events is adequate. There are no recommendations for further study needed for this indication. The sponsor should continue to monitor postmarketing adverse events as is required in 21 CFR § 314.50 (d)(5)(vi)(b).

7.2.8 Assessment of Quality and Completeness of Data

The sponsor has presented a complete safety profile and complete data.

7.2.9 Additional Submissions, Including Safety Update

The sponsor should continue to monitor postmarketing adverse events as is required in 21 CFR § 314.50 (d)(5)(vi)(b).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

- There are no new drug-drug interactions presented in the CLOT study.

7.4 General Methodology

- Not applicable.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

- Not applicable.

7.4.1.1 Pooled data vs. individual study data

- Not applicable.

7.4.1.2 Combining data

- Not applicable.

7.4.2 Explorations for Predictive Factors

- Not applicable.

7.4.2.1 Explorations for dose dependency for adverse findings

- Not applicable.

7.4.2.2 Explorations for time dependency for adverse findings

- Not applicable.

7.4.2.3 Explorations for drug-demographic interactions

- Not applicable.

7.4.2.4 Explorations for drug-disease interactions

- Not applicable.

7.4.2.5 Explorations for drug-drug interactions

- Not applicable.

7.4.3 Causality Determination

- Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dose of dalteparin that was used in the study was 200 IU/kg/day SC for the first month followed by 150 IU/kg/day SC for an additional 5 months for a total treatment period of 6 months. All dosing was capped at a maximum of 18,000 IU/d. This dosing schema was previously studied by the sponsor in the trials to determine the efficacy and safety of dalteparin in the treatment of VTE. A dose of 200 IU/kg SC qd was found by the sponsor to best balance benefit and risk in the setting of acute VTE management.

8.2 Drug-Drug Interactions

- No new drug-drug interactions were reported.

8.3 Special Populations

- The sponsor proposes that dalteparin be indicated for use in cancer patients who develop VTE and are thereby at increased risk for thromboembolism in the period following the initial therapy of VTE.[2,3] The CLOT study supports the use of long term (6 months) of dalteparin treatment in this group of patients. The results are consistent when analyzing the frequency of first adjudicated VTE by disease characteristics at baseline except for 2 subgroups of patients. In patients with hematologic malignancies, 4/40 (10%) in the dalteparin arm developed recurrent VTE compared to 0/30 (0%) in the OAC arm. In patients with non-metastatic cancer 7 of 115 (6.1%) in the dalteparin arm and 5/106 (4.7%) in the OAC arm developed recurrent VTE.

Table 24. Frequency of First Adjudicated VTE by Disease Characteristics at Baseline (ITT Population)

Factor	Dalteparin N=338			OAC N=338		
	Pts at risk	Pts with VTE	%	Pts at risk	Pts with VTE	%
ECOG performance status						
0	80	7	8.8	63	7	11.1
1	135	8	5.9	150	21	14.0
2	118	12	10.2	122	24	19.7
3	5	0	0	3	1	33.3
Type of tumor						
Solid	298	23	7.7	308	53	17.2
Hematological	40	4	10.0	30	0	0
Type of solid tumor						
Breast	59	2	3.4	49	2	4.1
Gastrointestinal	79	7	8.9	85	14	16.5
Lung	40	5	12.5	50	18	36.0
Genitourinary	77	4	5.2	78	10	12.8
Other	43	5	11.6	46	9	19.6
Extent of solid tumor						
Non metastatic†	75	3	4.0	76	5	6.6
Metastatic	223	20	9.0	232	48	20.7
Prior antineoplastic medication						
Yes	217	17	7.8	194	28	14.4
No	121	10	8.3	144	25	17.4
Prior radiotherapy						
Yes	58	4	6.9	56	10	17.9
No	280	23	8.2	282	43	15.2
Prior surgery						
Yes	37	2	5.4	50	6	12.0
No	301	25	8.3	288	47	16.3

† In the Table T6.5, which reported the levels of each prognostic factor as used in the Cox model for the primary outcome, the level non-metastatic also included the 70 patients with hematologic tumors (40 dalteparin patients and 30 OAC patients)

Source: Table T6.5 of CLOT Clinical Study Report (Module 5.3.5.1).

- Dalteparin was superior in reducing VTE compared to OAC across all ages, and in both males and females. There were too few non-caucasians in the study to demonstrate effectiveness in those populations.

Table 23. Frequency of First Adjudicated VTE by Demographic Characteristics (ITT Population)

Factor	Dalteparin N=338			OAC N=338		
	Pts at risk	Pts with VTE	%	Pts at risk	Pts with VTE	%
Age at entry						
<50 years	48	7	14.6	53	14	26.4
50-<60 years	84	8	9.5	75	10	13.3
60-<70 years	103	10	9.7	96	18	18.8
70+ years	103	2	1.9	114	11	9.6
Gender						
Male	159	15	9.4	169	33	19.5
Female	179	12	6.7	169	20	11.8
Race						
White	322	26	8.1	322	51	15.8
Black	7	1	14.3	8	1	12.5
Asian or Pacific Islander	7	0	0	3	0	0
Mixed	1	0	0	1	0	0
Not Allowed to Ask	0	0	0	2	1	50.0
Missing	1	0	0	0	0	0
Other	0	0	0	2	0	0

Source: Table T6.5 of CLOT Clinical Study Report (Module 5.3.5.1), Appendix 2.7.3: Table 3 of Module 2.7.3.

- Analysis of the results by country found that in the 3 countries with the greatest recruitment, i.e. Canada, Australia and USA, the effect of treatment favored the dalteparin arm. The effect of treatment was not apparent in those countries with a small number of patients recruited (<40 per group) and is likely due to the low number of observed DVT recurrence events. The table below shows the results of first adjudicated VTE by country.

Table 22. Frequency of First Adjudicated VTE by Country (ITT Population)

Factor	Dalteparin N=338			OAC N=338		
	Pts at risk	Pts with VTE	%	Pts at risk	Pts with VTE	%
Country						
Canada	126	10	7.9	129	20	15.5
Australia/New Zealand	81	7	8.6	79	18	22.8
US	58	3	5.2	60	8	13.3
Italy	34	4	11.8	33	4	12.1
The Netherlands	22	2	9.1	19	2	10.5
Spain	16	1	6.3	17	1	5.9

Source: Table T6.5 of CLOT Clinical Study Report (Module 5.3.5.1).

8.4 Pediatrics

No pediatric patients were included in the study. The sponsor (b) (4)

(b) (4)

8.5 Advisory Committee Meeting

- Not applicable.

8.6 Literature Review

- See references.

8.7 Postmarketing Risk Management Plan

- Not applicable.

8.8 Other Relevant Materials

- Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

The administration of dalteparin subcutaneously, 200 IU/kg qd (maximum 18,000 IU) for a period of 1 month followed by 150 IU/kg (maximum 18,000 IU) qd for a period of 5 months for a total of 6 months of therapy appears to be effective in the treatment and prophylaxis of VTE in cancer patients when compared to the use of dalteparin 200IU/kg qd for a period of 5-7 days with the combination of oral anticoagulant with enough overlap time for the INR to reach and maintain a therapeutic range of 2-3. The rate of recurrent VTE was 8.0% (27/338 patients) in the dalteparin arm compared to 15.7% (53/338 patients) in the OAC arm. The primary comparison of the cumulative probability of first VTE recurrence over the 6 month study period was statistically significantly different (2 sided log rank test, p=.0017). There was a 52% reduction in the risk of VTE recurrence over 6 months in the dalteparin arm compared to the OAC arm. The fact that dalteparin given for 5-7 days in the OAC arm may favor the dalteparin only arm may be due to the fact that there may be inadequate anticoagulation during the period of maximum thrombogenicity (i.e. approximately 3 months after the development of a VTE in patients with cancer)[4] as well as the fact that there were more highly thrombogenic type tumors in the OAC arm compared to the dalteparin arm in this study.

The safety of dalteparin compared to OAC in the treatment of patients with cancer who develop VTE can be summarized as follows:

1. In the dalteparin arm, 13.6% of patients had any bleeding compared to 18.5% of patients in the OAC arm.

2. In the dalteparin arm, 5.6% of patients had at least 1 major bleeding event compared to 3.6% in the OAC arm.
3. Discontinuation of treatment because of bleeding occurred in 3.0% in the dalteparin arm compared to 5.7% in the OAC arm.
4. a. Major bleeding event rates were similar for both arms in the first week of treatment when both groups were on similar doses of dalteparin (1.2%).
   b. In weeks 2-4 of the study (during the period of time that patients in the dalteparin arm were continued on 200 IU/kg sc qd while OAC arm patients were on vitamin K anatagonist), major bleeding occurred in 2.7% of patients in the dalteparin arm compared to 0.3% of patients in the OAC arm.
   c. From week 5 to the completion of the study, the major bleeding rate was similar in the 2 treatment arms (3.0%).
5. a. Four and one half percent of patients in the dalteparin arm and 2.1% of patients in the OAC arm experienced thrombocytopenia that was believed to be related to study medication.
   b. A decrease in platelet count was the reason for treatment modification or interruption in 8.0% in the dalteparin arm and 1.5% of patients in the OAC arm.
   c. Thrombocytopenia was the reason for discontinuation of treatment in 1.5% of patients in dalteparin arm and 0.3% of patients in the OAC arm.
6. Patients in the dalteparin arm had slightly more frequent liver enzyme (AST, ALT, ALP, GGT) and bilirubin elevations compared to patients in the OAC arm.
7. The other AE's and SAE's were similar in the 2 treatment arms.

The rates of death between the treatment arms were similar at 6 and 12 months (131 dalteparin vs. 137 OAC arm and 188 dalteparin vs. 192 OAC arm respectively). The cumulative probability of death over 6 and 12 months for the 2 treatment groups was not statistically significantly different. The majority of patients in both groups died due to progression of their underlying malignancy (90.8% dalteparin vs. 90.5% OAC arm). The frequency of death due to non-malignancy related causes was 3.6% in the dalteparin arm and 3.9% in the OAC arm. Fatal bleeding was the cause of death in 3 patients in the dalteparin arm and 1 patient in the OAC arm.

9.2 Recommendation on Regulatory Action

The indication sought by the sponsor for the treatment of symptomatic VTE (proximal DVT and/or PE) and to reduce the frequency of recurrent VTE in patients with cancer is approvable using dalteparin in above stated dosing regimen. This recommendation is based on the data provided by the sponsor in this submission.

9.3 Recommendation on Postmarketing Actions

- Not applicable.

9.3.1 Risk Management Activity

- Not applicable.

9.3.2 Required Phase 4 Commitments

- Not applicable.

9.3.3 Other Phase 4 Requests

- Not applicable.

9.4 Labeling Review

- The sponsor has submitted proposed labeling changes that would be included in a new label for dalteparin based on the data of the CLOT study.
- The following changes to the sponsor's proposed label should be made:

a. "Patients with Cancer and Acute Symptomatic Venous Thromboembolism" – this section essentially describes the CLOT study and would describe the dosing used along with the salient efficacy points.
b. A statement that dalteparin is indicated for the extended treatment of symptomatic VTE in patients with cancer.
c. Changes in the geriatric use section that includes the number of patients that were 65 and 75 years or older respectively from the CLOT study.
d. A table that demonstrates the timing of VTE recurrence in the CLOT study and a table that captures the bleeding events observed in the CLOT study.
e. A statement regarding the other adverse events that were reported in >10% of patients in either arm of the CLOT study.
f. Instructions to physicians regarding the dosing of dalteparin in cancer patients with modifications to the dosing in patients with obesity, renal insufficiency and thrombocytopenia.
g. Changes to the labeling that involve packaging changes.

9.5 Comments to Applicant

The indication sought by the sponsor is approvable, provided the recommended changes are made in the proposed labeling.

10 APPENDICES

10.1 Review of Individual Study Reports

- Not applicable.

10.2 Line-by-Line Labeling Review

- Not Applicable.

REFERENCES

[1] Prandoni, P. et al.: Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100:3484-3488.
[2] Levine, M.N. et al.: Thrombosis in Cancer Patients. ASCO 2002 Education Book. Perry, M.C. ed. Alexandria, 2002. p. 57-60.
[3] Bick, R.L.: Cancer-associated thrombosis. NEJM. 2003; 349(2)p. 109-111.
[4] Hyers, T.M. et al.: Antithrombotic therapy for venous thromboembolic disease. Chest. 2001. 119(1S): p. 176S-193S.

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

Date: April 26, 2007

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader for Hematology
Division of Medical Imaging and Hematology Products (HFD-160)

Subject: Medical Team Leader Secondary Review
Amendment to NDA 20-287/SE1-035 (3rd review cycle); submitted 2/28/07
Fragmin (dalteparin sodium) Injection

Efficacy supplement to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer

To: NDA 20-287

This is the third review cycle for this supplemental NDA application seeking approval of Fragmin (dalteparin sodium) for a new indication of "extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer." The proposed treatment regimen is dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for one month followed by dalteparin, approximately 150 IU/kg (maximum 18,000 IU) s.c. once daily for 5 additional months (total 6 months).

Currently approved indications for Fragmin include thromboprophylaxis in several clinical settings (i.e., hip replacement surgery patients, abdominal surgery patients at risk for thromboembolic complications, and medical patients at risk for thromboembolic complications due to restricted mobility during acute illness) with treatment duration for up to 14 days.

To support the new indication a single controlled clinical trial (The CLOT Study) was provided. This was an open-label, randomized (1:1), multicenter, parallel groups, active control superiority design study conducted in 676 cancer patients presenting with an acute episode of objectively confirmed proximal lower limb DVT, PE or both comparing the dalteparin regimen above ("dalteparin arm") to a regimen of dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for 5-7 days while receiving concomitant oral vitamin K antagonist (OAC, usually warfarin) therapy until the INR reached 2-3, at which time the dalteparin was discontinued and oral anticoagulation was continued for the remainder of 6 months with a target INR of 2-3 ("OAC arm"). CLOT Study results showed that significantly fewer patients in the dalteparin arm experienced recurrent VTE during the 6 months treatment as compared to patients in the OAC arm (8.0% (27/338) vs. 15.7% (53/338), respectively; p=0.0017), with most of the treatment difference evident in the first month. There were some inconsistencies in overall efficacy results with higher VTE rates in the Fragmin arm in patients with hematologic malignancies and in patients with non-metastatic cancer than in the OAC arm and there were more study drug discontinuations due to death in the Fragmin arm as compared to the OAC arm. More patients in the Fragmin arm than in the OAC

arm experienced major bleeding. See previous Medical Reviews (Dr. A. Dmytrijuk, signed 1/14/05; Dr. G. Shashaty, signed 1/14/05; Dr. K. Robie-Suh, signed 1/14/05; Dr. A. Dmytrijuk, 3/8/06, signed 3/13/06; Dr. K. Robie-Suh, 3/13/06), Statistical Review (Milton Fan, Ph.D., signed 12/2/04) and action letters for the first two review cycles (1/14/05; 3/14/06) for additional details regarding the study results and deficiencies.

In this submission the sponsor has provided a complete response to the not approvable (NA) letter issued on 3/14/06. Major deficiencies cited in the NA letter concerned an imbalance in deaths while on study drug treatment with excess deaths in the Fragmin arm as compared to the OAC treatment arm, concerns regarding inadequate minimization of bias in this open label study which may have led to differential discontinuation of patients in the two treatment arms, and concerns of inconsistent primary endpoint results among patients with supposedly non-metastatic cancer and patients with hematologic cancers. The NA letter requested that the sponsor conduct an additional adequate and well-controlled study employing stringent methods to minimize bias to address these concerns. Additional investigation was also requested for the indication in cancer patients with renal impairment and in pediatric cancer patients. The application, including CLOT Study design and results, was presented and discussed at a meeting of the Oncology Drugs Advisory Committee (ODAC) on 9/6/06 and the committee unanimously recommended approval of the new indication.

The current submission contains revised labeling and a safety update and includes proposed post-marketing commitments for two studies: a study to assess the long-term (>6months) safety of Fragmin administration and this study would also include patients with renal impairment (including severe renal impairment) and a study to assess the safety and efficacy of Fragmin in pediatric patients with cancer. The Medical Officer's Review (Dr. A. Dmytrijuk, completed 4/12/07, signed 4/26/07) states "A review of the provided safety update for the period of March 2005 to March 2006 reveals no new safety concerns". The review recommends:

- Approval of the application for the indication "for the extended treatment of symptomatic venous thromboembolism (VTE) to prevent recurrent VTE in patients with cancer" with the dosing regimen studied in the Fragmin arm in the CLOT study.

- That the sponsor submit protocols for and conduct two post-marketing studies as follows:
    - A study "to assess the safety of Fragmin administration for periods of time en excess of six months and also assess the safety of Fragmin use in patients with cancer and renal impairment including severe renal impairment."
    - A study to "assess the safety and efficacy of Fragmin in pediatric patients with cancer who require anticoagulation and include all ranges of pediatric patients."

- Some changes to the sponsor's proposed labeling. Importantly, in the CLINICAL STUDIES section and ADVERSE REACTIONS section describing the results of the CLOT study, some modifications to the section describing dose adjustments for thrombocytopenia in patients with cancer and acute symptomatic VTE and dose reductions for renal insufficiency in extended treatment of acute symptomatic VTE in cancer patients, wording of the indication stated as "Fragmin is also indicated for the extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer." (See labeling

attached in the Medical Officer's Review (Dr. A Dmytrijuk, completed 4/12/07, signed 4/26/07).

Previous Medical Officer Review (Dr. A. Dmytrijuk, 1/14/05) addressing the sponsor's request (b) (4) [redacted]

Conclusions:
The supplemental application for the new indication stated as "for the extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer" should be approved. Recommended dosing is dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for one month followed by dalteparin, approximately 150 IU/kg (maximum 18,000 IU) s.c. once daily for 5 additional months.

There should be the following post-marketing commitments:

1. To conduct a study to evaluate the safety and efficacy of dalteparin in cancer patients (both metastatic and non-metastatic) receiving extended treatment with dalteparin (>6 months) for prevention of new or recurrent symptomatic VTEs, including subjects with renal impairment (including severe renal impairment).

2. To evaluate efficacy and safety of dalteparin in pediatric cancer patients who require anticoagulation. Studies using dalteparin for VTE treatment in all age ranges of the pediatric population should be performed.

Labeling revisions should be made as recommended in the Medical Officer's Review (Dr. A. Dmytrijuk, completed 4/12/07, signed 4/26/07).

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/s/

Kathy Robie-Suh
4/26/2007 06:49:35 PM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 13, 2006

From: Kathy M. Robie-Suh, M.D., Ph.D.
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Division of Medical Imaging and Hematology Products (HFD-160)

Subject: Medical Team Leader Secondary Review
Amendment to NDA 20-287/SE1-035; submitted 9/14/05
Fragmin (dalteparin sodium) Injection

Efficacy supplement to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer

To: NDA 20-287

Background:
This is the second review cycle for this supplemental NDA application in which the sponsor is seeking approval of Fragmin (dalteparin sodium) for the indication of "extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer." There are currently no anticoagulants approved for this specific indication. Although approved for thromboprophylaxis in several clinical settings (i.e., hip replacement surgery patients, abdominal surgery patients at risk for thromboembolic complications, and medical patients at risk for thromboembolic complications due to restricted mobility during acute illness), Fragmin has not been studied for and is not approved for short-term treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Also, treatment duration for the proposed new indication is for 6 months. Currently, no low molecular weight heparin is labeled for a treatment duration longer than 35 days.

This efficacy supplement was submitted on 3/16/04. The supplement consisted of a single open-label, randomized (1:1), multicenter, parallel groups, active control superiority design study (Study 98-FRAG-069; CLOT Study) conducted in 677 (676 treated) cancer patients presenting with an acute episode of objectively confirmed proximal lower limb DVT, PE or both. The treatments were: "dalteparin arm" [dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for one month followed by dalteparin, approximately 150 IU/kg (maximum 18,000 IU s.c. once daily for 5 additional months (total 6 months)], and "OAC [oral anticoagulant] arm" [dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for 5-7 days while receiving concomitant oral vitamin K antagonist (OAC, usually warfarin) therapy until the INR reached 2-3, at which time the dalteparin was discontinued and oral anticoagulation was continued for the remainder of 6 months with a target INR of 2-3]. Study results showed that significantly fewer patients in the

dalteparin arm experienced recurrent VTE during the 6 months treatment as compared to patients in the OAC arm (8.0% (27/338) vs. 15.7% (53/338), respectively; p=0.0017 for cumulative probability of first VTE recurrence over the 6-month treatment period [2-sided log-rank test]). However, subgroup analysis found the results to be inconsistent among subgroups of country, type of tumor (solid vs. hematological), extent of tumor, and previous VTE. No differences between treatment groups were found in mortality during the 6 months treatment or during the followup period (to 12 months). Statistical review (Milton Fan, Ph.D., signed 12/2/04) concluded evidence of efficacy in this study alone was not statistically persuasive. Clinical review of the study concluded that efficacy was adequately demonstrated for the overall population but additional safety and efficacy information was desired regarding use of dalteparin in VTE patients with hematological tumors, non-metastatic tumors, cancer and renal dysfunction, and pediatric cancer patients as well as additional safety information on dalteparin use at higher doses and for longer durations, particularly with regard to liver function. (See Medical Officer Review by Dr. A. Dmytrijuk, signed 1/14/05; Acting Medical Team Leader secondary review by Dr. G. Shashaty, signed 1/14/05; Acting Deputy Division Director Memorandum by Dr. Kathy Robie-Suh, signed 1/14/05). An approvable letter was issued on 1/14/05 reflecting these deficiencies.

In the current amendment the sponsor has responded to the approvable letter. In addition, further examination of the mortality data for the CLOT study by the review team during the current review cycle found that, although the time to death and overall mortality at end of 6 months treatment and end of followup (12 months) were similar in the two treatment arms, there appeared to be a higher rate of "on treatment" deaths in the dalteparin arm as compared to the OAC arm. The review evaluation of the new mortality finding and the sponsor's responses to the approvable letter are summarized below. See also Dr. A. Dmytrijuk's Medical Officer's Review (completed 3/8/06, signed 3/13/06).

Additional Examination of Mortality in the CLOT Study:
Overall mortality in the CLOT Study was high with 38.8% of patients in the Fragmin arm and 34.6%% of patients of in the OAC arm dying by 6 months and 56.2% of patients in the Dalteparin arm and 57.9% of patients of in the OAC arm dying by 12 months. The overall rate of death was similar in the two treatment arms. However, while overall proportions of deaths were similar in the two treatment arms, there appeared to be an excess of deaths while on treatment in the dalteparin treatment arm at 6 months (59/338; 17.5%) as compared to in the OAC treatment arm (21/335; 6.3%). The difference between treatment arms in "on treatment" deaths is apparent in the sponsor's table below:

Table 46. Summary of Deaths (As-treated Population)

Primary Cause of Death	Dalteparin N=338						OAC N=335					
	On Treatment		Off treatment		Total		On Treatment		Off treatment		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	59	17.5	131	38.8	190	56.2	21	6.3	173	51.6	194	57.9
Patients with adjudicated reason of death (first 6 months)												
All	59	17.5	72	21.3	131	38.8	21	6.3	116	34.6	137	40.9
Underlying cancer	54	16.0	65	19.2	119	35.2	14	4.2	110	32.8	124	37.0
Fatal PE	4	1.2	2	0.6	6	1.8	5	1.5	3	0.9	8	2.4
Fatal bleeding	1	0.3	2	0.6	3	0.9	0	0.0	1	0.3	1	0.3
Other	0	0.0	3	0.9	3	0.9	2	0.6	2	0.6	4	1.2
Patients without adjudicated reason of death (from 6 to 12 months)												
All	—	—	59	17.5	59	17.5	—	—	57	17.0	57	17.0
Underlying cancer	—	—	45	13.3	45	13.3	—	—	45	13.4	45	13.4
Infection	—	—	5	1.5	5	1.5	—	—	3	0.9	3	0.9
Cardiac disorders	—	—	3	0.9	3	0.9	—	—	0	0.0	0	0.0
Renal disorders	—	—	3	0.9	3	0.9	—	—	1	0.3	1	0.3
Respiratory disorders	—	—	1	0.3	1	0.3	—	—	1	0.3	1	0.3
Fatal bleeding	—	—	0	0.0	0	0.0	—	—	1	0.3	1	0.3
Other	—	—	1	0.3	1	0.3	—	—	3	0.9	3	0.9
Unknown	—	—	1	0.3	1	0.3	—	—	3	0.9	3	0.9

Abbreviations: OAC = oral anticoagulant
Source: Tables T7.13, and T9.7; Appendix 3.6.3

In both treatment arms, most deaths (on or off treatment) were attributed to "underlying cancer" (first 6 months: 119/131 [90.8%] in the dalteparin arm and 124/137 [90.5%] in the OAC arm; 6 to 12 month followup: 45/59 [76.3%] in the dalteparin arm and 45/57 [78.9%] in the OAC arm). Also, most of the "on treatment" deaths were attributed to underlying cancer (54/59 [91.5%] deaths in the dalteparin arm and 14/21 [66.7%] deaths in OAC arm). VTE (i.e., fatal PE) accounted for 4/59 [6.8%]of "on treatment" deaths in the dalteparin arm and 5/21 [23.8%] of "on treatment" deaths in the OAC. Fatal bleeding at any time during the study occurred in only 3 patients in the dalteparin arm and 2 patients in the OAC arm.

The higher rate of "on treatment" death is also reflected in the reasons for discontinuation from study treatment. The sponsor's table showing disposition of patients in the CLOT Study is shown below:

Table 12. Reasons for Discontinuation (As-treated Population)

	Dalteparin N=338		OAC N=335		Total N=673	
	N	%	N	%	N	%
Patients who completed treatment	180	53.3	163	48.7	343	51.0
Patients who discontinued	158	46.7	172	51.3	330	49.0
Death	56	16.6	24	7.2	80	11.9
Underlying cancer	52	15.4	17	5.1	69	10.3
Fatal PE	3	0.9	5	1.5	8	1.2
Fatal bleeding	1	0.3	0	0.0	1	0.1
Other	0	0.0	2	0.6	2	0.3
Confirmed acute VTE	21	6.2	47	14.0	68	10.1
DVT	12	3.6	35	10.4	47	7.0
PE	7	2.1	10	3.0	17	2.5
CVT of upper limb	2	0.6	2	0.6	4	0.6
Contraindication to anticoagulation	12	3.6	25	7.5	37	5.5
Bleeding	10	3.0	19	5.7	29	4.3
Other	1	0.3	6	1.8	7	1.0
Missing	1	0.3	0	0.0	1	0.1
Adverse event	17	5.0	19	5.7	36	5.3
Abnormal bloodwork	4	1.2	4	1.2	8	1.2
Abnormal investigation results	1	0.3	1	0.3	2	0.3
Patient decision / withdrawal of consent	20	5.9	14	4.2	34	5.1
Other	27	8.0	38	11.3	65	9.7
Underlying cancer	17	5.0	21	6.3	38	5.6
Investigator decision	1	0.3	5	1.5	6	0.7
Patient unable to swallow	0	0.0	4	1.2	4	0.6

Abbreviations: CVT = central venous thrombosis; DVT = deep vein thrombosis; OAC = oral anticoagulant; PE = pulmonary embolism; VTE = venous thromboembolic event
Source: Table T1.4, Appendix 3.1.1, 3.1.2, and 3.6.3

Appendix 3.1.1 contains a listing of subjects that discontinued from the study.

Overall, in the dalteparin arm 53.3% (180/338) of patients completed study treatment as compared to 48.7% (163/335) in the OAC arm. "On treatment" death was the major cause for discontinuation from study treatment in the dalteparin arm while confirmed acute VTE was the major cause for treatment discontinuation in the OAC arm. In the dalteparin arm 6.2% (21/338) of patients discontinued study treatment because of a VTE and in the OAC arm 14.0% (47/335) of patients discontinued study treatment because of a VTE. Percentages of patients discontinuing study treatment for reasons other than death and/or VTE were 24.0% (81/338) in the dalteparin arm and 30.1% (101/335) in the OAC arm. Over the 12 month study period, fatal bleeding leading to death occurred in 3 patients in the dalteparin group (1 on treatment) and 2 patients in the OAC group (0 on treatment).

Overall, in the study the median durations of treatment in the two treatment arms were similar (176 days in the dalteparin arm and 167 days in the OAC arm). However, the duration of treatment for patients who died differed in the two groups. The timing of deaths in relation to whether or not they were on study treatment is summarized in the following table for all treated patients:

CLOT Study: Timing of Deaths During Entire 12-Month Followup (As Treated Population[@])[#]

	Dalteparin (N=338)			OAC (N=335)		
	N	%		N	%	
Patients who Completed treatment[^]	180	53.3		163	48.7	
Patients who discontinued[^]	158	46.7		172	51.3	
Discontinuation due to deaths[^]	56	16.6		24	7.2	
All deaths	190	56.2		194	57.9	
Deaths on treatment	59	17.5		21	6.3	
Mean time to death (days)			*70.3*			*45.6*
Median time to death (days)			*56*			*26*
Range (days)			*1-173*			*2-116*
Deaths within 30 days of d/c treatment	64	18.9		78	23.3	
Mean time to death (days)			*90.0*			*73.5*
Median time to death (days)			*66.5*			*51*
Range (days)			*10-215*			*4-232*
Deaths after 30 days of d/c treatment	67	19.8		95	28.4	
Mean time to death (days)			*227.1*			*183.3*
Median time to death (days)			*241*			*187*
Range (days)			*45-382*			*42-368*

[#]days are from first day in study; [@] 4 patients randomized to the OAC arm were never treated;
[^] during 6-month treatment period

Reviewer's table based on sponsor's Table 12, p.47 of report for Study 98-FRAG-069; Table 46, p. 89 of report for Study 98-FRAG-069, and Appendix 3.6.3 Listing for Study 98-FRAG-069

Patients in the dalteparin arm who died tended to have received treatment with study drug for a longer period of time than had patients in the OAC arm who died. The median duration of treatment at time of on treatment death in the dalteparin arm was 56 days (mean 70.3 days; range 1-173 days) as compared to 26 days (mean 45.6 days; range 2-116 days) in these patients in the OAC arm. Proportion of patients dying within 30 days of discontinuing study treatment was a

bit greater in the OAC arm (78/335 [23.8%]) than in the dalteparin arm (65/338 [19.2%]). As shown in the table below, at any given time during the study the proportion of deaths on treatment tended to be greater in the dalteparin arm than in the OAC arm.

CLOT Study: Any and "On Treatment" Deaths by Time on Study*

Period (days)	Dalteparin treatment arm				OAC treatment arm			
	N	Any Deaths during period, n (%)	On treatment deaths during period, n (%)	On treatment deaths during period/total deaths during period	N	Any Deaths during period, n (%)	On treatment deaths during period n (%)	On treatment deaths during period/total deaths during period
0-30	338	26 (7.7)	17	0.65	338	31 (9.2)	11	0.35
31-60	311	35 (11.25)	15	0.43	304	33 (10.9)	3	0.09
61-90	275	26 (9.5)	9	0.35	270	27 (10.0)	4	0.15
91-120	249	12 (4.8)	3	0.25	242	20 (8.3)	3	0.15
121-150	237	17 (7.2)	10	0.59	221	10 (4.5)	0	0
151-180	220	14 (6.4)	5	0.36	211	15 (7.1)	0	0
Total (0-180)	338	130 (38.5)	59	0.45	338	136 (40.2)	21	0.15

*N=number of patients on treatment at beginning of period

Reviewer's table based on information from sponsor's Table 12, p.47 of report for Study 98-FRAG-069; Table 46, p. 89 of report for Study 98-FRAG-069, and Appendix 3.6.3 Listing for Study 98-FRAG-069 and sponsor's table e-mailed 2/24/06

The number and proportion of on treatment deaths in the dalteparin arm tended to be greatest during the first two months of the study treatment. During the first 30 days of study participation 14 of the 17 "on treatment" deaths in the dalteparin group were attributed to underlying cancer as compared to 5 of 11 "on treatment" deaths in the OAC arm. During this same time, VTE accounted for 3 "on treatment" deaths in the dalteparin arm and 5 "on treatment" deaths in the OAC arm.

Reviewer's comments: The importance of the observation of more "on treatment" deaths with dalteparin in the CLOT Study is unclear. In the first 6 months on study "on treatment" deaths accounted for 45.0% (59/131) of all deaths in the dalteparin arm but only 15.3% (21/137) of all deaths in the OAC arm. At 12 months the numbers were 31.1% (59/190) for the dalteparin arm and 10.8% (21/194) for the OAC arm. Because the study was open-label, this result may have been affected by the decision to terminate or not terminate study treatment. The two treatments being compared in the CLOT study are quite disparate in some general features. For example, dalteparin is injected s.c. while OAC (mostly warfarin) is given orally; OAC has numerous and well-known problems with drug interactions and maintenance of anticoagulation within therapeutic range while dalteparin is much less subject to these problems. Issues such as these may have led to continuation of dalteparin in patients who might have been discontinued had continued anticoagulation required use of warfarin. [That such might have been the case is suggested by the observation that among patients who died on treatment, duration on treatment tended to be longer in the dalteparin arm (median, 56 days) than in the OAC arm (median, 26 days)]. Thus, the potential introduction of bias by the decision to discontinue treatment may have affected the outcome of the study with regard to "on treatment" and "off treatment" deaths. The study plan did not provide for collection of the detailed information that would be needed to more closely examine reasons for discontinuation of study medication. Consequently, in the CLOT study the higher rate of "on treatment" death in the dalteparin arm is irredeemably confounded with the decision to discontinue (or not) study treatment. In effect, we cannot with

the available information determine whether or not the observed higher "on treatment" death rate in the dalteparin arm reflects a true effect of or association with dalteparin treatment.

Sponsor's Responses to Deficiencies in the 1/14/05 Approvable Letter :
To address the concerns about safety of dalteparin for longer duration of treatment and higher doses, the sponsor submitted a safety update for Fragmin (dalteparin sodium) incorporating safety data accrued 10/31/03 (cutoff for the CLOT study submission (S-035)) through 3/15/05. There were no new studies of dalteparin for the indication currently being sought. Safety data from 5 new studies were submitted. These included a total of 591 patients and involved protocol-specified treatment durations up to 2 months. An additional study for initial inpatient versus outpatient treatment of VTE is ongoing (Study 041, being conducted in Italy, of dalteparin 5-9 days followed by OAC). In that study there have been 4 discontinuations due to adverse events, 7 patients experienced serious adverse events (1 bleeding, 1 thrombocytopenia [also led to discontinuation]) and there was 1 death (due to pneumonia)(unclear total number of patients enrolled so far). In addition, there was one thromboprophylaxis observational study in 400 high risk post-surgical patients receiving dalteparin for up to 5 weeks. The sponsor reports there were no serious adverse events or deaths reported for this study. Dalteparin treatment duration was shorter and dose was less in these studies than in the CLOT Study. Incidence of bleeding events in the new studies was in keeping with the current labeling. On treatment serum chemistries (including hepatic transaminases) were not collected for the new clinical trials, except in a single-dose study in 26 subjects to evaluate dalteparin pharmacokinetics in renal insufficiency. The new safety information was generally consistent with the current Fragmin labeling and did not contribute significant new information for the use of dalteparin for extended thromboprophylaxis in cancer patients.

In the approvable letter the sponsor also was asked to commit to post-marketing studies to evaluate the safety and efficacy of dalteparin for the indication: in patients with cancer who have varying degrees of renal impairment, in patients with hematologic malignancies, and in patients with non-metastatic tumors. To better characterize risk for the longer duration of dalteparin use in these patients, the sponsor was asked to provide summary and analysis by treatment duration and dalteparin dose of measures of hepatic function, including hepatic transaminases, bilirubin, and other measures and to provide this information separately for chronically or severely ill patients and for patients who are not chronically ill. Draft labeling also was provided in the approvable letter.

The sponsor's responses have been reviewed by the Medical Reviewer (Dr. A. Dmytrijuk, review completed 3/8/06, signed 3/13/06). Sponsor's responses and Medical Reviewer comments are summarized briefly below:

- The sponsor declines to perform a study in cancer patients with renal failure for the indication stating that severity of illness and recruitment problems pose a hardship to the feasibility of doing such a study. Also, the sponsor provided a post-hoc subset analysis of the CLOT study in which they found that results in patients with renal failure were similar to those in the overall CLOT study. Though patients with severe renal impairment (serum creatinine 3 x upper limit of normal) were excluded from study participation, 161 patients with some degree of renal impairment (CrCl <60 mL/min) were enrolled in the study. Nine of these patients in the dalteparin arm and 5 in the OAC arm had CrCl <30 mL/min.

Recurrent VTE in patients with renal impairment occurred in 2/74 (3%) patients in the dalteparin arm and in 15/88 (17%) of patients in the OAC arm. Major bleeding occurred in 7/74 (9.5%) of patients in the dalteparin arm and in 6/87 (6.9%) of patients in the OAC arm. Overall, in the patients with renal impairment slightly more OAC patients had any bleeding as compared to dalteparin patients (21/87 [24.1%] vs 15/74 [20.3%]). Among patients with moderate renal impairment at study entry, proportions of patients whose renal function worsened during the study were similar (11/65 [16.9%] in the dalteparin arm and 11/82 [13.4%] in the OAC arm). The sponsor felt that with these analyses no further investigations in patients with renal impairment are necessary. The Medical Reviewer (Dr. A. Dmytrijuk, review completed 3/8/06, signed 3/13/06) found the sponsor's response "appears to be acceptable". The efficacy and safety finding of the subset analyses in patients with some degree of renal impairment were generally consistent with the overall study results. Because patients with significant renal impairment were excluded from study participation, it is not clear how representative the patients with renal impairment identified in the sponsor's post-hoc analyses are of the general population of cancer patients with renal impairment.

- The sponsor notes the agency's observation that patients with hematologic malignancies had a higher rate of VTE recurrence on dalteparin (i.e., in the study VTE rates at 6 months were 4/40 [10.0%] for the dalteparin arm and 0/30 [0%] for the OAC arm). The sponsor attributes this to the small size of the hematologic tumor population (about 10% of all patients) in the study and to an imbalance for this population in the two treatment arms and to a some imbalance favoring OAC in some VTE risk factors between the two treatment groups, including poor performance status, markers of advanced disease, major surgery and central venous catheters, hematologic cancers and lymphoma, smokers, and male gender. The sponsor found only one imbalance in favor of dalteparin arm – a higher median age. The sponsor proposes to address this concern in the labeling, reporting the VTE result and stating that the study was not designed for analysis of VTE rates by tumor type. Also, the sponsor indicates that due to a relatively low incidence of patients with hematologic cancer and VTE, feasibility of such a study would be limited by a slow enrollment rate, which could result in a failure to complete the study. In his review Dr. Dmytrijuk (review completed 3/8/06, signed 3/13/06) found that in 3 of the 4 cases of VTE in hematologic cancer patients in the dalteparin arm, the risk factors mentioned by the sponsor appeared to favor the OAC arm and "may explain the discrepancy between the two treatment arms in the CLOT study".

- The sponsor notes the agency's observation that patients with non-metastatic tumors seem to have a higher rate of VTE recurrence on dalteparin. In the study VTE rates at 6 months were 7/115 [6.1%] for the dalteparin arm and 5/106 [4.7%] for the OAC arm in patients with non-metastatic cancer as contrasted with rates of 20/223 [9.0%] and 48/232 [20.7%] in the dalteparin and OAC groups, respectively, for patients with metastatic cancer. The sponsor agrees to conduct a post-marketing study to further evaluate the safety and efficacy of the use of dalteparin in patients with non-metastatic cancer and VTE and provides a clinical protocol synopsis for a study. The study would enroll about 790 patients with confirmed solid malignancy and appearing to be non-metastatic. It would be stratified for tumor type and Performance Score. Study treatments and endpoints would be the same as for the CLOT Study. The Medical Reviewer (Dr. A. Dmytrijuk, review completed 3/8/06, signed 3/13/06)

found this response not acceptable, stating that the study would be open-label similar to the CLOT Study and would not be powered to perform any sub-analysis based on tumor type. The proposed study should have a randomized, double-blind, double dummy design. The full protocol should be submitted for review.

- The sponsor declines to perform a study in pediatric patients citing small number of patients and disinclination of patients to enroll in trials other than for anti-cancer treatments. The sponsor cites estimated rates of 5.3 per 10,000 hospital admissions in children 28 days to 16 years of age as compared to an incidence of 2.5-5.0% in the adult population. Based on a 1994 report from a Canadian Registry of VTE, the sponsor estimates a VTE rate of 0.07 per 10,000 children and states that "Of the 137 children entered into the registry, only 31 had cancer, which suggests that the incidence rate of VTE in pediatric cancer patients (in Canada) would be closer to 0.015 per 10,000 children." The sponsor asserts that the pediatric population and the disease are sufficiently similar in adult and pediatric patients that effectiveness of dalteparin for the indication in pediatrics can be extrapolated from the adult population, supplemented with other information obtained in pediatric patients, such as clinical pharmacology studies.

  The sponsor proposes to (b) (4) [redacted] The Medical Officer's review finds the sponsor's response inadequate and recommends that the sponsor should conduct a clinical trial to establish correlation between anti-Xa levels and clinical outcomes.

The sponsor also declines to conduct a study to explore transitioning a patient from dalteparin to an oral anticoagulant (i.e., to assure adequate anticoagulation during transition period), stating that this should be done by an oral anticoagulant sponsor and commenting that dosing and treatment management guidelines (e.g., American College of Chest Physicians) are widely available to the practice community.

Discussion:
On the face of it, the efficacy of dalteparin as used in the dalteparin treatment arm of the CLOT Study for preventing recurrence of VTE in the general population of cancer patients with VTE appears clear. There was a statistically significant decrease in recurrent VTE in the dalteparin treatment arm as compared to the comparator with VTE rates at 6 months of 8.0% (27/338) in the dalteparin arm as compared to 15.7% (53/338) in the comparator arm. The primary comparison of the cumulative probability of first VTE recurrence over the 6-month study period was statistically significant (2-sided log-rank test, p=0.0017). Unfortunately, however, in this open-label study, though the overall death rates during the study and at 6 and 12 months were similar for the two treatment arms, there was a disproportionately greater incidence of deaths while on treatment in the dalteparin arm. There were 59 "on treatment" deaths in the dalteparin arm as compared to 21 "on treatment" deaths in the OAC arm. Cause of death in most of these cases was attributed to underlying cancer and few of these patients (4 patients in the dalteparin arm and 5 patients in the OAC arm) had experienced recurrent VTE. Though these "on treatment" deaths represent a minority of the total deaths in the study, this imbalance strongly indicating a higher "on treatment" death rate for the dalteparin arm may effectively offset any benefit of dalteparin in preventing recurrent VTE. This observation may be attributed in part to a somewhat longer duration of treatment for the "on treatment" deaths in the dalteparin arm; however, this consideration alone is not adequate to account for the majority of the discrepancy. Indeed, there could be an as yet unrecognized mortality risk associated with use of dalteparin in these patients. Because the CLOT Study was an open-label trial, bias may have been introduced in making the decision to discontinue a patient from study treatment. For example, dalteparin was given s.c. while OAC treatment required the patient to swallow a tablet. Dalteparin is relatively free of significant drug-drug interactions, while OAC has many. Issues such as these may have led to continuation of dalteparin in clinically deteriorating patients who might have been discontinued had continued anticoagulation required use of warfarin, thus leading to more "on treatment" deaths in the dalteparin arm. The available database does not include sufficient granularity to allow determination of the precise events and considerations leading up to the decision to withdraw a patient from study treatment; therefore, the CLOT Study is irredeemably confounded in this regard. An additional clinical trial of adequate and well-controlled design employing stringent methods to minimize bias (i.e., blinding, double-double dummy control, use of sham INRs) is needed both to confirm clinically meaningful efficacy of dalteparin for this use and to clarify any possible effect of dalteparin on mortality in this population.

The sponsor has not provided any new data to address the concerns expressed in the approvable letter.
Renal impairment: No additional data are provided for use of dalteparin for the indication in cancer patients with renal impairment. Though the efficacy and safety results in the CLOT study for patients with renal impairment were similar to those of the overall population, there was a tendency to a higher incidence of bleeding with increasing degree of renal impairment and numbers of patients with renal impairment in the study were small. Also, because the study excluded patients with significant degrees of renal impairment (by serum creatinine), the patients in the study may not be representative of the larger population of cancer patients with renal impairment. The sponsor should consider allowing enrollment of patients with moderate renal impairment into any additional study they may conduct for this indication.

Hematologic cancers: The sponsor has reasonably addressed the observed higher rate of recurrent VTE in dalteparin group than in the oral anticoagulant group in the patients with hematologic cancers. This population was only a small percentage of the total study population and there may have been a cumulative imbalance in hematologic patient numbers and VTE risk factors that led to the higher number of VTEs in the dalteparin group. Patients with hematologic cancers should be included in any additional study the sponsor may conduct for the indication; however, the sponsor should consider stratifying for hematologic cancers.

Non-metastatic tumors: The sponsor has agreed to conduct a post-marketing study in patients with non-metastatic tumors. However, the design of the sponsor's proposed study is inadequate. Considering the need that has been identified for an additional efficacy and safety study for the desired indication before marketing approval of dalteparin for the indication, the sponsor could consider expanding this study to allow analysis both for confirmation of efficacy and safety in the total cancer population and evaluation of efficacy and safety in the subset of non-metastatic tumors. The sponsor should submit a proposal for a study for review.

Pediatric patients: The sponsor proposes (b) (4) The study as currently designed is not likely to provide adequate information to label dalteparin for pediatric use. The sponsor's assertion that (b) (4) (b) (5) However, in general pediatric patients do suffer VTE events and information on use of anticoagulants, including dalteparin, in these patients is needed. Therefore, the sponsor should be encouraged to pursue an appropriate expanded pediatric development plan for dalteparin.

Conclusion and Recommendation:
The sponsor is seeking approval of Fragmin (dalteparin sodium) for the extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer. For the first review cycle the sponsor submitted a single, open-label clinical trial of dalteparin for 6 months compared to dalteparin followed by oral anticoagulant for 6 months.(the CLOT Study). The study demonstrated a lower rate of recurrent VTE for patients in the dalteparin treatment arm as compared to patients in the oral anticoagulant treatment arm at 6 months with overall similar mortality at 6 and 12 months. Further examination of the study results during this second cycle review has identified a serious safety concern of excess deaths on treatment in the dalteparin arm as compared to the oral anticoagulant arm that cannot be resolved within the existing trial. Though these deaths represent a minority of the total deaths, they are comparable in frequency to the incidence of recurrent VTE and call into question the relative benefit-risk of the dalteparin treatment as well as possibly the validity of the efficacy result. Therefore, the available information is not adequate to allow approval of this efficacy supplement.

To gain approval for the indication, the sponsor must:

1. Design and conduct an additional adequate and well-controlled clinical trial to confirm clinically meaningful efficacy of dalteparin for this use and to clarify any possible effect of dalteparin on mortality in this population. The trial should employ stringent methods to minimize bias (i.e., blinding, double-double dummy control, use of sham INRs). The target population should be enrolled (i.e., the broad population of all cancer patients with VTE). Because the CLOT study showed disparate results for patients with non-metastatic tumors and patients with hematologic cancers, consideration should be given to stratifying for these factors. The study protocol should be submitted for review.

2. Design and conduct an adequate and well-controlled study of sufficient size to analyze the efficacy and evaluate safety of dalteparin for this indication in the sub-population of cancer patients with non-metastatic tumors. The study protocol should be submitted for review.

In addition, because numbers of patients with renal impairment studied to date are limited and those studied may not be representative of cancer patients with renal impairment, the sponsor should consider conducting a study for the indication in patients with moderate renal impairment. Lack of adequate information for this population should be reflected in restrictions for use in labeling.

Finally, the sponsor should propose a development plan to investigate efficacy and safety of dalteparin in pediatric patients who require anticoagulation.

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/s/

Kathy Robie-Suh
3/13/2006 04:54:40 PM
MEDICAL OFFICER

M E M O R A N D U M

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

Date: January 14, 2005

From: Kathy M. Robie-Suh, M.D., Ph.D.
Acting Deputy Director
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Subject: NDA 20-287/SE1-035; submitted 3/16/04
Fragmin (dalteparin sodium) Injection

Efficacy supplement to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer

To: NDA 20-287

Fragmin is a low molecular weight heparin (LMWH) approved (initial approval 12/22/94) for prophylaxis of deep venous thrombosis (DVT), which may lead to pulmonary embolus (PE) in: hip replacement surgery patients, abdominal surgery patients who are at risk for thromboembolic complications, and medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness. Fragmin is also approved for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction (MI), when concurrently administered with aspirin.

In the current supplemental application the sponsor has submitted one multicenter, randomized, open-label, parallel groups, active control, superiority design study (Study 98-FRAG-069; CLOT Study) in cancer patients with an acute episode of objectively confirmed proximal lower limb DVT, PE or both to support the indication of "extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer." The study enrolled 676 consenting patients (intention-to-treat population) who were randomized equally to the following treatment arms:

- Fragmin arm: dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for one month followed by dalteparin, approximately 150 IU/kg (maximum 18,000 IU s.c. once daily for 5 additional months (total 6 months), or
- OAC arm: dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for 5-7 days while receiving concomitant oral vitamin K antagonist (OAC, usually warfarin) therapy until the INR reached 2-3, at which time the dalteparin was discontinued and

oral anticoagulation was continued for the remainder of 6 months with a target INR of 2-3.

The OAC arm treatment regimen was chosen based on its being a current standard of care. Subjects enrolled in the study were patients age >16 years with active malignancy who are diagnosed with acute, symptomatic proximal lower limb DVT, PE or both, objectively confirmed. Important exclusion criteria were conditions conferring increased risk for bleeding, poor performance status (ECOG status of 3-4), body weight ≤40 kg, significant renal failure, platelet count <75 x 10^9/L, pregnancy or inadequate contraception. The study was designed to demonstrate superiority of the Fragmin arm treatment regimen over the OAC arm treatment regimen for the primary efficacy endpoint of recurrence of symptomatic VTE of the leg(s) or lung during the 6-month study period.

Of the enrolled patients, about 90% of patients had solid tumors (most commonly breast, gastrointestinal or lung). About 10% of patients had hematologic cancers. Baseline characteristics were reasonably well balanced between the two treatment arms. FDA Statistics review (Milton Fan, Ph.D., 12/2/04) found that the Fragmin arm regimen was superior to the OAC arm regimen in reducing the risk of recurrent symptomatic VTE. Time-to-first-event analyses were described using the Kaplan-Meier method for each treatment group and were compared using the log rank test. The Statistical Review states: "A total of 27 of 338 patients randomized to dalteparin (8.0%) and 53 of 338 patients randomized to OAC (15.7%) experienced at least one adjudicated, symptomatic DVT and/or PE during the 6-month study period. The primary comparison of the cumulative probablity of first VTE recurrence over the 6-month study period was statistically significant (2-sided log-rank test, p=0.0017). There was a significant reduction of 52% in the risk of VTE recurrence over 6 months in the dalteparin as the risk ratio of dalteparin to OAC was 0.48 (95% CI, 0.30-0.77, likelihood ratio test, p=0.0016)." The lower recurrent VTE rate in the Fragmin arm was due mainly to a marked reduction in DVT (4.1% in the Fragmin arm as compared to 10.9% in the OAC arm) while the difference with regard to PE was much more modest (3.8% in the Fragmin arm as compared to 4.7% in the OAC arm). Results were similar for the as treated population. There was some inconsistency in results across countries, solid versus hematological tumor, extent of tumor and previous VTE. No difference was demonstrated with regard to survival. The evidence for efficacy provided by the CLOT study alone was found to be not statistically persuasive.

Most of the difference in incidence of VTE events between treatment arms was seen during the second through fourth weeks of study treatment. For weeks 2-4 rates of recurrent VTE were 1.8% in the Fragmin arm and 7.6% in the OAC arm. The Medical Officer's Review (Andrew Dmytrijuk, M.D., 01/14/05) proposes that the level of anticoagulation in the OAC arm during the period immediately following the 5-7 days of dalteparin in the OAC arm may have been inadequate treatment for the heightened thrombogenicity of the early period after development of VTE in patients with cancer and

therefore biased the study in favor of the Fragmin arm where high dose dalteparin (200 IU/kg) was continued for a full month.

The dose of dalteparin proposed for the indication being sought is higher than the doses currently in the Fragmin label (which at this time includes only prophylactic indications). Also, the duration of dosing proposed (6 months) is longer than the labeled duration of dosing for any of the LMWH drugs. The higher dalteparin dose for the treatment indication is understandable considering the well-understood need for greater anticoagulant effect during the acute phase of treatment of an existing VTE. In the CLOT study the extended treatment duration is adequately supported as providing a continued therapeutic benefit in these patients. However, the existing clinical safety database contains limited information on the safety of dalteparin at these higher doses and for 6 months or longer duration.

The Medical Officer's Review (Andrew Dmytrijuk, M.D., 1/14/05) indicates that the safety profile of dalteparin in this study was comparable to the control arm in the overall frequency of adverse events, treatment discontinuations for drug-related adverse events, and frequency of serious adverse events. However, the patients in this study were ill with cancer and, not unexpectedly, there were a large number of deaths (55% of patients in the Fragmin arm and 58% of patients in the OAC arm) and adverse events during the 6-months study duration. Therefore, the ability to discern differences in adverse event profiles between the two treatments in the study was limited. During the 6 months on study, more patients had major bleeding in the Fragmin arm (6.0%) as compared to the OAC arm (4.0%); however, more patients in the OAC arm had any bleeding (18.5%) as compared to the Fragmin arm (13.6%). The Medical Officer's review states that the rate of bleeding was slightly higher in the dalteparin arm (3.8%) compared to the OAC arm (1.5%) in the first 4 weeks of the study. Treatment emergent Grade 3-4 elevation of LFTs (chiefly gamma-glutamyl transpeptidase (GGT) in this study) during the study was seen in 18.3% of patients in the Fragmin arm and 16.9% of patients in the OAC arm. Most of these patients in both treatment arms continued and completed study treatment and outcomes were similar to those seen in the overall population. Elevation of hepatic transaminases has been seen in other studies of heparin and LMWHs.

Other Information:
Other Clinical: Division of Scientific Investigation (DSI) inspected one site (Michael Kovacs, M.D., London Health Science Center; London, Ontario, Canada) for this study. Two minor good faith violations were found and the site was found to be well-onducted and supervised (Khairy W. Malek, M.D., Ph.D., 12/9/04).

The sponsor has submitted (letter date 3/25/04) a request (b) (4) for the indication being sought. The request has been reviewed and recommendation

made for denial [redacted] (b) (4) (See Medical Officer's review, Andrew Dmytrijuk, M.D., 01/14/05).

Chemistry, Manufacturing and Controls (CMC): This supplement also provides for registration of four new syringe presentations consisting of 10000 IU (anti-Factor Xa)/0.4 ml, 12500 IU (anti-Factor Xa)/0.5 ml, 15000 IU (anti-Factor Xa)/0.6 ml, and 18000 IU (anti-Factor Xa)/0.72 ml single dose syringe. The CMC information to support the new presentations was found to be adequate (Chemistry review, Ali Al-Hakim, Ph.D., 12/2/04). Microbiology review found the sponsor's decision to withdraw a proposal to use [redacted] (b) (4) and instead use [redacted] (b) (4) according to validated and approved processes at the Vetter Pharmaa-Fertigung manufacturing facility acceptable (Stephen Langille, 1/4/05). Establishment Evaluation Request (EER) report was found to be acceptable (11/5/04).

Preclinical Pharmacology and Toxicology: There was no preclinical pharmacology and toxicology information in this submission.

Clinical Pharmacology and Biopharmaceutics:
No new human pharmacokinetic (PK) data were submitted and no revisions to the human PK section of the labeling were proposed by the sponsor. The supplement was found acceptable from Office of Clinical Pharmacology and Biopharmaceutics perspective (Tien-Mien Chen, Ph.D., 11/29/04).

Conclusions and Recommendations:
In conclusion, the CLOT study has demonstrated a benefit and acceptable safety of dalteparin 200 IU/kg s.c. daily given for 1 month followed by dalteparin 150 IU/kg s.c. given daily for 5 additional months in extended treatment of acute DVT and/or PE in patients with cancer to reduce the recurrence of VTE in these patients. The benefit of the treatment was most clearly seen during the first month of treatment when for most of the time patients in the OAC arm were just reaching and being stabilized on their OAC dose while patients in the Fragmin arm were receiving high dose dalteparin. The available data do not permit evaluation of the adequacy of anticoagulation during the time when patients in the OAC arm were being transitioned from dalteparin + OAC to OAC alone. Therefore, superiority of the Fragmin regimen over adequate OAC for the indication has not been clearly established. Nevertheless, the Fragmin arm regimen used in this study appears to provide a meaningful clinical benefit with an acceptable safety profile in this indication. The major safety concern for Fragmin in this population is bleeding. As stated in the Secondary Clinical Review (George Shashaty, M.D., 1/14/05), "The current trial is the only available study of dalteparin that provides data for the indication in the population described, but there are a number of studies that indicate its efficacy and safety in the prevention of VTE in other populations." Therefore, Fragmin in the proposed regimen should be made available as a therapeutic option for cancer patients with acute symptomatic VTE and appropriate information to direct its use should be included in the labeling. With regard to the CLOT study, the labeling should reflect that:

- The major benefit of the Fragmin regimen appeared during the first month of treatment.
- Patients with hematologic malignancies in the Fragmin arm tended to have more recurrent VTE events as compared to these patients in the OAC arm. However, these patients represented only about 11% of randomized patients and numbers of events were small.
- There was a higher rate of bleeding during the first month with Fragmin as compared to OAC arm.
- There was no difference in mortality between the two treatment arms of the study.
- Patients with significant renal failure were excluded from the study. There is inadequate information to support the dosing adjustment proposed in the sponsor's labeling for these patients.
- The information available in the submission is inadequate to recommend specific dosing reduction in patients who develop thrombocytopenia on Fragmin; therefore, the table included by the sponsor in the Dosage and Administration section titled "Dose Reduction of Fragmin for Thromboyctopenia 50,000-100,000/mm^3" should not be included in the labeling.

In the **Clinical Trials** section of the labeling care should be taken to clearly describe the treatment regimens being compared in the CLOT study. In addition, numbers and descriptions of patients studied and findings should be updated in the following sections of the labeling: **WARNINGS, Thrombocytopenia**; **Precautions, Drug/Larboratory Test Interactions:** ***Elevations of Serum Transaminases***; **Precautions, Geriatric Use**; **Adverse Events, Other:** ***Ongoing Safety Surveillance.***

The sponsor should provide summary and analysis by treatment duration and Fragmin dose of data from the Fragmin safety database, including evaluations of hepatic transaminases, bilirubin and other measures of liver function to assess safety of dalteparin at the doses and for the duration proposed for the indication being sought. To more accurately assess possible risk, information on higher doses and longer treatment durations from studies where patients are not chronically ill should be summarized separately from information from chronically or severely ill patients.

Commitment should be obtained from the sponsor to conduct the following post-marketing studies as described in the Medical Team Leader's secondary review (George Shashaty, M.D., 01/14/05). These commitments include:

1. The sponsor should design and conduct a study to further evaluate the effectiveness and safety of Fragmin for treatment and reduction of recurrence of VTE in patients with hematologic cancers.

2. The sponsor should design and conduct a study to further evaluate the effectiveness and safety of Fragmin for treatment and reduction of recurrence of VTE in patients with non-metastatic cancers.

3. The sponsor should design and conduct a study to evaluate the effectiveness and safety of Fragmin for treatment and reduction of recurrence of VTE in patients with cancer and having varying degrees of renal impairment.

4. The sponsor should propose and carry out a plan to address use of Fragmin for the extended treatment of symptomatic VTE in pediatric patients with cancer.

In addition, the sponsor should consider further studies to investigate how best to transition patients from Fragmin to oral anticoagulation, should that change in therapy become necessary for a patient. The CLOT study data suggest and the sponsor has discussed (fax of 1/13/05) that patients being transitioned to OAC may be inadequately protected against recurrent thrombosis, due to pharmacodynamic issues related to time course of depletion of Vitamin K dependent coagulation factors and Proteins C and S.

Additional comments and recommendations from the Medical Officer's Review (Andrew Dmytirjuk, M.D., 1/14/05) and the secondary medical review (George Shashaty, M.D., 01/14/05) should be considered.

cc:
NDA 20-287
HFD-180/DMoore
HFD-180/GShashaty
HFD-180/KRobie-Suh
HFD-720/Sgrosser
HFD-720/MFan
HFD-180/JChoudary
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/s/

Kathy Robie-Suh
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MEDICAL OFFICER

MEMORANDUM

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

Date: January 7, 2004

From: George G. Shashaty, M.D.
Acting Medical Team Leader, Hematology
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

Subject: Medical Team Leader Secondary Review
NDA 20-287 (SE 035), submitted March 16, 2004
Fragmin (dalteparin sodium)

To: NDA 20-287

Background

Fragmin (dalteparin sodium) is a low molecular weight heparin produced through controlled nitrous oxide depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. Its molecular weights (b) (4) the parent compound with a mean molecular weight of 5000 Daltons, with 90% of the material within the range of 2000 to 9000 Daltons. Dalteparin has an anti-thrombotic effect as a consequence of its ability to alter the conformational structure of the naturally occurring anti-coagulant, Antithrombin III (AT III). AT III is a serine protease inhibitor that inactivates a number of the activated components of the coagulation system thereby reducing clotting. Dalteparin interacts with AT III to preferentially inhibit Factor Xa compared to unfractionated heparin.

Dalteparin was first approved for use in the United States in December, 1994 and is currently approved for the following indications:

- The prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
    1. In patients undergoing hip replacement surgery.
    2. In patients undergoing abdominal surgery who are at risk for thromboembolic complications.
    3. In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

- The prophylaxis of ischemic complications in unstable angina and non-Q wave myocardial infarction, when concurrently administered with aspirin therapy.

The administration of dalteparin is by the subcutaneous route and the dose is either fixed or based on body weight, depending on indication. At the doses administered, there is little effect on the prothrombin time (PT) or the activated partial thromboplastin time (aPTT). Therefore, routine laboratory studies are not performed to control its dosing. When indicated, the effect of dalteparin on blood coagulation has been performed by measuring anti-Xa levels after administration of the drug. After subcutaneous administration of dalteparin, peak anti-Xa levels are seen at approximately 4 hours, and the terminal half-life is 3 to 5 hours. The terminal half-life is prolonged in patients with renal failure.

The major adverse event associated with the administration of dalteparin is hemorrhage. Its use is contraindicated in patients with active major bleeding and in those patients diagnosed with heparin induced thrombocytopenia. The label contains a black box warning for epidural and spinal hematoma formation with potential paralysis when dalteparin is given in chronological relationship to epidural catheters and lumbar puncture. Precaution for its use is recommended in patients with a bleeding diathesis, thrombocytopenia, qualitative platelet defects, hepatic and renal insufficiency, hypertensive and diabetic retinopathy, and recent gastrointestinal bleeding.

Current Submission

The sponsor seeks approval for the following indication:

- Dalteparin (FRAGMIN®) is indicated for the extended treatment of symptomatic VTE (proximal DVT and/or PE) to prevent recurrent VTE in patients with cancer.

In support of the indication, the sponsor has submitted a single study referred to as Study 98-FRAG-069, whose acronym is the CLOT study. This was a randomized, open-label, active-control, multi-center, multinational trial comparing a regimen of dalteparin alone (dalteparin arm) to a purported standard-of-care (dalteparin for 5 to 7 days concurrent with, and followed by, warfarin therapy [OAC arm]) for 6 months to treat and prevent the recurrence of DVT and/or PE in patients with cancer.

In this study, 677 patients were randomized with 338 entering into the dalteparin arm and 339 entering into the OAC arm. One patient in the OAC arm did not have informed consent and was excluded from the trial, providing 338 intention-to-treat patients in each arm. Three patients in the OAC arm received no therapy so the as-treated population in the OAC arm was 335.

Patients with objectively demonstrated (compression ultrasound, venogram, high probability ventilation/perfusion lung scan, spiral CT or pulmonary angiography) acute, symptomatic proximal lower limb DVT and/or PE were eligible for the study if they also had any of:

- Cancer diagnosed within 6 months prior to entry.
- Having received cancer treatment in the 6 months prior to entry.
- Currently receiving cancer treatment.
- Having evidence of metastatic disease.

Patients were excluded for a number of reasons, the most pertinent of which included:

- Weight <40 kg.
- ECOG status of 3 and 4.
- Recent hemorrhage or increased potential to bleed.
- Thrombocytopenia with a platelet count <75,000/mm^3.
- Plasma creatinine greater than 3 times the ULN.

After randomization, patients were treated in one of two arms:

- Dalteparin arm. Dalteparin, 200 IU/kg (maximum 18,000 IU) s.c. once daily for one month, followed by dalteparin, 150 IU/kg (maximum 18,000 IU) s.c. once daily for 5 additional months (total 6 months).
- OAC arm. Dalteparin, 200 IU/kg (maximum 18,000 IU) s.c. once daily for 5-7 days while receiving concomitant oral vitamin K antagonist (usually warfarin) therapy until the INR reached 2-3, at which time the dalteparin was discontinued and oral anticoagulant was continued for the remainder of 6 months with a target INR of 2-3.

Patients were then followed for the development of clinical symptoms and signs of VTE and for adverse events. If clinical suspicion of VTE was raised, objective confirmation (similar to the studies noted above) was required to confirm an endpoint of recurrent DVT and/or PE. The efficacy endpoint was the first occurrence of an adjudicated confirmed DVT and/or PE during the 6 month study period. Secondary endpoints included the addition of central venous thrombosis and overall survival at 6 and at 12 months.

Demographic characteristics of the populations in the 2 arms of the trial were reasonably equally distributed for age (median, 64 years), sex (approximately equal males and females), weight (median, 74 kg), ECOG performance status and tumor status (no evidence, local, metastatic). The distribution of tumor types suggested a somewhat higher frequency of more thrombogenic tumors (GI, lung and brain) in the OAC arm (43.4%) compared to the dalteparin arm (37.6%) and a somewhat higher frequency of less thrombogenic tumors (breast) in the dalteparin arm (17.5%) compared to the OAC arm (14.5%).

Patients randomized to the dalteparin arm received a median daily dose of 198 IU/kg during the first month of the study, and 162 IU/kg for the remainder of the 6 months. The mean proportion of patients randomized to the OAC arm were within the target INR of 2 to 3 in 51.4 %, above an INR of 3 in 24.6% and below an INR of 2 in 24% of total treatment time. The duration of treatment was longer

in the dalteparin arm because of a greater frequency of the development of VTE in the OAC arm, particularly during the first month, and this remained the case throughout the 6 months of the study.

In the analysis of the intention-to-treat population, the overall rate of symptomatic VTE in the dalteparin arm was 8.7% (27/338) and that in the OAC arm was 17.2% (53/338), (p=0.0017). The efficacy of dalteparin in reducing VTE was most noticeable during the first 4 weeks of the study when patients in the dalteparin arm continued to receive full dose therapy. By the end of that period, VTE rates were 3.3% in the dalteparin arm compared to 10.1% in the OAC arm. During the remainder of the trial, the rates were 6.3% and 8.3%, respectively. Most recurrent VTE in both treatment arms were DVTs of the lower extremities (4.4% for dalteparin, 11.2% for OAC). The frequencies for PE (dalteparin, 3.0%; OAC 3.3%) and fatal PE (dalteparin, 1.8%; OAC, 2.4%) were no different between the two groups. The overall rates of death at 6 months (dalteparin, 38.8%; OAC, 40.5%) and at 12 months (dalteparin, 55.6%; OAC, 56.8%) were also no different between the two groups. Most of the deaths were attributable to progression of the cancer.

Major bleeding events were more common in the dalteparin arm (2.7%) compared to the OAC arm (0.3%) during weeks 2 through 4, during which time patients in the dalteparin arm continued to receive 200 IU/kg daily. In week 1 and during weeks 5 through 26, the frequency of major bleeding was comparable (dalteparin, 4.2%; OAC, 4.2%). Minor bleeding was higher in the OAC arm (14.9%) compared to the dalteparin arm (8.9%). Only 1 fatal bleeding episode occurred while patients were on study drugs, and that was from hemoptysis in a patient with lung cancer who was receiving dalteparin. Three additional deaths secondary to bleeding were reported in the dalteparin arm and 1 in the OAC arm, but these occurred after the patients had discontinued anticoagulant therapy. Ten patients in the dalteparin arm and 5 in the OAC arm permanently discontinued anticoagulation therapy because of a major hemorrhagic event. Thrombocytopenia considered to be drug related occurred more frequently in the dalteparin arm (4.5%) compared to the OAC arm (2.1%). Other adverse events, whether believed related or unrelated to study drug administration, were reasonably comparable between the 2 groups except for a somewhat greater frequency of abnormal hepatic enzyme elevations seen in patients treated with dalteparin. Such elevations were generally of a modest degree were not associated with additional significant clinical events.

A statistical review of Study 98-Frag-069 was performed by Dr. Milton Fan and finalized on December 2, 2004. He concluded that while the study did demonstrate the superiority of dalteparin compared to OAC in the reduction of recurrent DVT and/or PE in cancer patients, there were several subgroups in which the results were anomalous. These included patients with hematological malignancies (dalteparin, 10% [4/40 patients]; OAC, 0% [0/30 patients]) patients with non-metastatic cancer (dalteparin, 6.1% [7/115]; OAC, 4.7% [5/106]) and

patients with a previous history of venous thromboembolism (dalteparin, 8.6% [3/35]; OAC, 6.3% [2/32]). These findings may have been related to the infrequency of recurrent VTE in both treatment arms of the trial in these subgroups. Dr. Fan noted that there was no difference in survival between the two treatment groups. He concluded that the evidence of efficacy from this single study was not statistically persuasive, and that the results had not been replicated in another trial. The current trial is the only available study of dalteparin that provides data for the indication in the population described, but there are a number of studies that indicate its efficacy and safety in the prevention of VTE in other populations.

An evaluation of a single study site (London Health Science Centre, London, Ontario, Canada) by the Division for Scientific Investigations found minor good faith errors and concluded that the data from the study could be used in support of the NDA supplement.

A review performed by the Clinical Pharmacology and Biopharmaceutics Division concluded that the supplement was acceptable to them.

There were no new Pharmacology/Toxicology data provided. The only CMC issue was the addition of several new single-dose syringe dosing formulations.

Conclusions

The study performed by the sponsor in support of the requested indication appears to demonstrate that dalteparin is reasonably safe and effective in treating and reducing the frequency of recurrent VTE in patients with cancer who are diagnosed with VTE. Although this is a single study submitted in support of the indication, the studies that led to its other approved indications provide additional support based on mechanism of action and similarity of disease entity (VTE). There are, however, several precautions that should be noted in recommending this therapeutic approach to such patients including:

- The use of dalteparin does not improve survival.
- The use of dalteparin seems to reduce the frequency of recurrent DVT of the lower extremities. It has not been shown to decrease the frequency of pulmonary embolism nor of death from pulmonary embolism.
- Dalteparin does not appear to be beneficial, and may even be detrimental, in the treatment and reduction of recurrent VTE in patients with hematological malignancies. In patients with non-metastatic cancer and in patients with cancer with a previous history of VTE, dalteparin may not be more effective than OAC in reducing VTE in patients with cancer.
- Although the frequency of recurrent VTE may be diminished by the administration of dalteparin during the first month of treatment when the

dose of the drug is 200 IU/kg daily compared to OAC, there is no significant difference in the rate of recurrent VTE compared to OAC during the succeeding 5 months of therapy when the dose of dalteparin is reduced to 150 IU/kg. Therefore, the effectiveness of the long term use of dalteparin beyond the first month of treatment for VTE compared to OAC may be equivalent rather than superior even though the trial was designed as a six month study.

- The administration of a dose of 200 IU/kg daily during the first month of therapy increases the frequency of major bleeding when compared to the administration of OAC given over the same time period.
- Treatment emergent and drug related thrombocytopenia are more common with the administration of dalteparin than with OAC. This may impair the ability to provide appropriate chemotherapy and radiotherapy to cancer patients treated with dalteparin.
- The convenience of the oral administration of OAC is diminished by the inconvenience of the need for periodic performance of a PT. The inconvenience of parenteral administration of dalteparin is counterbalanced by the elimination of the need for laboratory monitoring..
- Clinicians should be aware that the reduction in recurrence of DVT of the lower extremities associated with the administration of dalteparin compared to OAC in cancer patients is counterbalanced by a greater frequency of major bleeding primarily during the first month of therapy, and that the use of dalteparin compared to OAC does not increase survival, diminish the frequency of, nor death due to, pulmonary embolism.
- The study does not provide data to evaluate the efficacy and safety of the use of dalteparin in patients with cancer whose serum creatinine is greater than 3 times the upper limit of normal for a laboratory.
- Although the study mandated dose reductions for dalteparin in patients whose platelet counts fell below 100,000/mm^3 and discontinuation of dalteparin for patients whose platelet count fell below 50,000/mm^3, the numbers of patients whose dose was altered were too few to determine the efficacy and safety of such dose alteration.
- Although the sponsor has conducted and provided summary data for studies that indicate that the administration of dalteparin once daily overlapped with OAC is equally effective as unfractionated intravenous heparin overlapped with OAC in the treatment of acute VTE, primary data are not available for review and treatment of acute VTE with dalteparin is not an approved indication in the United States.

Recommendations

The following indication should be approved:

- Dalteparin (FRAGMIN®) is indicated for the extended treatment of symptomatic VTE (proximal DVT and/or PE) to prevent recurrent VTE in patients with cancer.

The following post-marketing commitments should be sought:

- A study of the effectiveness and safety of the use of dalteparin in patients with hematological tumors who have developed VTE.
- A study of the effectiveness and safety of the use of dalteparin in patients with non-metastatic tumors who have developed VTE.
- A study of the effectiveness and safety of the use of dalteparin in patients with cancer and renal dysfunction who have developed VTE.

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/s/

George Shashaty
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MEDICAL OFFICER

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

NDA:	20,287
Sponsor:	Pfizer Inc. 235 East 42nd St. New York, NY 10017
Drug name:	Dalteparin (Fragmin)
Indication:	Extended treatment of symptomatic venous thromboembolism in patients with cancer.
Route of administration:	Subcutaneous
Date submitted:	March 25, 2004
Date received:	March 26, 2004
Review completed:	January 13, 2005
Reviewer:	Andrew Dmytrijuk, M.D.

1. Background and Rationale

In a submission dated March 25, 2004 the sponsor requests (b) (4) for the indication of extended treatment of symptomatic venous thromboembolism (VTE including, both deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) using dalteparin to prevent recurrent VTE in patients with cancer which is currently under review.

2. Chemistry/Pharmacology/Toxicology Summary

No new chemistry, pharmacology or toxicology information provided.

3. Previous Human Experience

Dalteparin was approved in the USA on December 22, 1994 for thromboprophylaxis in abdominal surgery for patients at risk for thromboembolic complications. Subsequently, dalteparin was approved for: DVT prophylaxis in patients undergoing hip replacement surgery (March 1999); prophylaxis of ischemic complications in unstable angina and non-Q wave myocardial infarction when concurrently administered with aspirin (May 1999); and DVT prophylaxis which may lead to PE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness (November 2003). Since it was first brought to market, an estimated (b) (4) patients have been prescribed dalteparin.

The sponsor states that the proposed indication of treatment and thromboprophylaxis of thromboses in the proximal lower limb and/or pulmonary embolism in cancer patients, with 6 months of dalteparin given as a subcutaneous injection of 200 IU/kg for 1 month followed by 150 IU/kg for the next 5 months, is seen rarely in the pediatric cancer population. The sponsor states that published clinical data indicate that the majority of pediatric venous thromboses occur in the upper venous system and that these thrombotic events are frequently associated with central venous catheters.[1,2] The sponsor further states that the reduced incidence of the disease of interest (proximal lower limb deep venous thrombosis and pulmonary embolism) combined with the relative rarity of childhood cancer makes clinical trials impractical.

In a meeting with the sponsor on October 28, 2003, in response to a request (b) (4)

Review of the literature indicates that venous thromboembolism (VTE) in pediatrics is becoming a recognized cause of significant morbidity and mortality in children. Most children diagnosed with VTE have a serious underlying primary illness such as cancer, chronic total parenteral nutrition (TPN) dependency, or congenital heart disease. Infants and adolescents are most at risk of developing VTE, and the most significant risk factor is the presence of a central venous line (CVL).[1] In a study of the Canadian Childhood Thrombophilia Registry which monitored 244 consecutive patients with objectively

diagnosed CVL-related DVT for a median duration of 24 months (range 3 months to 7 years), the incidence of CVL-related DVT was 3.5 per 10,000 hospital admissions. CVL-related DVTs were more frequent in the upper venous system.[2] The incidence of VTE varies widely with study design. However, little is known about the epidemiologic characteristics or outcome of CVL-related deep venous thrombosis (DVT).

Some studies have shown that there is a low, but not zero, rate of VTE in children with cancer. A study done in pediatric patients investigated the incidence and complications of VTE in pediatric neuro-oncology patients. This study retrospectively analyzed the files of all patients under the age of 18 years who were hospitalized for the treatment of brain tumors between the years 1990 and 2003 in two leading, closely related, Israeli neuro-oncology centers. In this study a total of 462 children were analyzed. Three hundred eighty-four patients underwent surgery and 78 were treated medically. Three (0.64%) of the patients developed clinical episodes of VTE that were treated conservatively. Two of these patients developed intracranial bleeding while on secondary prevention for the disease. Although this study has limitations because of its retrospective design, heterogeneous group of patients and diagnoses, the changing awareness for thrombosis over the last 14 years and the inclusion of symptomatic VTE events only, the data suggest that, as opposed to adults, the risk of clinically significant VTE in children with brain tumors may be low. These findings set the stage for future evaluations in view of the prospective studies that were done in adults and the possible significant implications for the prevention and possible etiologies of the disease.[3]

However even though the risk of VTE is less with some conditions, it is not negligible. A Canadian registry of VTE in children (ages 1 month to 18 years) was established July 1, 1990 in 15 tertiary- care pediatric centers. One-hundred thirty-seven patients were identified prospectively and were included in an analysis of the incidence of VTE in children. The incidence of deep vein thrombosis/pulmonary embolism (DVT/PE) was 5.3/10,000 hospital admissions or 0.07/10,000 children in Canada. Infants under 1 year of age and teenagers predominated. DVT were located in the upper (n = 50) and lower (n = 79) venous system, or as PE alone (n = 8). CVLs were present in approximately 33% of children with DVT (n = 45). Associated conditions were present in 96% of children and 90% of children had two or more associated conditions for DVT. Out of 137 patients included for analysis in this study 22.6% (n = 31) had cancer, 14.6% (n = 20) had congenital heart disease, 14.6% (n = 20) had VTE associated with trauma, while the remaining 48% (n = 66) had total parenteral nutrition, infection, nephrotic syndrome, surgery, birth-control pills, obesity, systemic lupus erythematosus, sickle cell anemia, liver failure, no cause or other listed as associated conditions. DVT was diagnosed by venography (n = 83), duplex ultrasound (n = 37), and other combinations (n = 17). Twenty-two of 31 ventilation/perfusion scans performed were interpreted as high-probability scans for PE. Therapy consisted of heparin (n = 115), thrombolysis (n = 15), surgical removal of a CVL or thrombus (n = 22), and oral anticoagulant therapy (n = 103). Significant bleeding complications did not occur. However, three (2.2%) children died as a direct consequence of their thromboembolic disease; DVT recurred in 23 children and postphlebitic syndrome (PPS) occurred in 26. Therefore, DVTs occur in a significant number of hospitalized children with a mortality of 2.2%. Complications are

not hemorrhagic, but thrombotic, and characterized by PE, recurrent disease, and PPS. In contrast to adults, the upper venous system is frequently affected because of the use of CVLs. This study concludes with the statement that the frequency of DVT/PE justifies controlled trials of primary prophylaxis in high-risk groups, and therapeutic trials to determine optimal treatment.[4]

4. Reviewer's Comments and Discussion

The sponsor requests that (b) (4) A review of the literature does not support this claim. Studies using dalteparin for VTE treatment and prophylaxis in all ranges of the pediatric population should be performed. Particular attention should be given to VTE treatment and prophylaxis using dalteparin in children with central venous line and cancer associated VTE.

5. Conclusions and Recommendations

(b) (4)

Studies should be performed to evaluate VTE treatment and prophylaxis using dalteparin in children with central venous line associated VTE. The sponsor should submit adequate and well controlled studies of the use of dalteparin in the treatment and reduction of recurrence of VTE in pediatric cancer patients

References:

[1] Anton, N and Massicotte, M.P.: Venous thromboembolism in pediatrics. Semin. Vasc. Med. 2001; 1(1):111-122.
[2] Massicotte, M.P. et al.: Central venous catheter related thrombosis in children: analysis of the Canadian Registry of Venous Thromboembolic Complications. J. Pediatr. 1998; 133(6):770-776.
[3] Tabori, U. et al.: Risk of venous thromboembolism in pediatric patients with brain tumors. Pediatr. Blood Cancer. 2004. 43(6): 633-636.
[4] Andrew, M. et al.: Venous thromboembolic complications (VTE) in children: First analyses of the Canadian Registry of VTE. Blood. 1994; 83(5):1251-1257.

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/s/

Andrew Dmytrijuk
1/14/05 04:15:30 PM
MEDICAL OFFICER

George Shashaty
1/14/05 04:21:37 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

CHEMISTRY REVIEW(S)

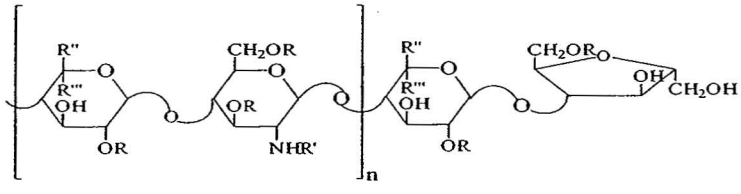
CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 20-287	
3. Name and Address of Applicant (City & State): Pharmacia & Upjohn 7000 Portage Road Kalamazoo, MI 49001-0199		4. AF Number: 5. Supplement(s)	
6. Name of Drug: Fragmin®	7. Nonproprietary Name: Deltaparin Sodium injection	Numbers	Dates
		SE1-035 BZ	March 16, 2004

8. Supplement Provides for:
Indication in the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The supplement is also provides for registration of four new syringe presentations consisting of 10 000 IU (anti-Factor Xa)/0.4 ml, 12 500 IU (anti-Factor Xa)/0.5 ml, 15000 IU (anti-Factor Xa)/0.6 ml, and 18000 **IU** (anti-Factor Xa)/0.72 ml single dose syringe. Manufacturing of the four new presentations will occur at the contract manufacturer Vetter Pharma-Fertigung, in Ravensburg, Germany. An (b) (4) [redacted] This may occur either at Vetter Pharma-Fertigung or at the supplier, in identical processes.

9. Amendments & Other (Reports, etc.) Dates:
Supplement/amendment dated July 29, 2004

10. Pharmacological Category: Anticoagulant	11. How Dispensed: RX X OTC	12. Related DMF(s):
13. Dosage Form: Solution for Injection	14. Potency: 2500 IU, 5000 IU, 10,000 IU, 25,000 IU and 7500 IU	

15. Chemical Name and Structure:
Sulfated polysaccharide chains at the non-reducing end and 6-O-sulfo-2, 5-anhydro-Dmannitol at reducing end.



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

16. Records and Reports:

Current Yes X No

Reviewed Yes X No

17. Comments: Satisfactory Establishment Evaluation Report (EER).
CC: NDA 20-287
HFD-180/Div File/NDA 20-287035
HFD-181/CSO/D. Moore
HFD-180/J.Korvick
HFD-180/A.Al-Hakim
HFD-180/ L. Zhou
12-02-04 /Wordfiles\S\20287035

18. Conclusions and Recommendations:
The supplement can be approved from CMC point of view, However, the microbiology consult regarding the (b) (4) [redacted] which was inspected by the FDA and found acceptable (see EER recommendation) is still pending.

19.Reviewer Name: Ali Al-Hakim, Ph.D.	Date Completed: 12/02/04

5 Page(s) Withheld

___X___ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

05-NOV-2004 FDA CDER EES

Page 1 of 1

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 20287/035
Org Code : 180
Priority : 1S

Sponsor: PHARMACIA AND UPJOHN
7171 PORTAGE RD
KALAMAZOO, MI 49001

Stamp Date : 17-MAR-2004
PDUFA Date : 17-JAN-2005
Action Goal :
District Goal: 13-DEC-2004

Brand Name : FRAGMIN
Estab. Name:
Generic Name: DALTEPARIN SODIUM
Dosage Form: (INJECTION)
Strength : 2500 & 5000 IU/.2ML

FDA Contacts: D. MOORE Project Manager (HFD-180) 301-827-7476

A. AL HAKIM Review Chemist (HFD-180) 301-827-7467

L. ZHOU Team Leader (HFD-180) 301-827-1251

Overall Recommendation: ACCEPTABLE on 01-NOV-2004by J. D AMBROGIO (HFD-322) 301-827-9049

ACCEPTABLE on 24-SEP-2004by S. ADAMS (HFD-322) 301-827-9051

Establishment: CFN : 9610708 FEI : 1000654629

PHARMACIA & UPJOHN COORDINATION CENTER

RIJKSWEG 12

PUURS, , BE

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-NOV-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment: CFN : 9610900 FEI : 3002270322

VETTER PHARMA FERTIGUNG GMBH AND CO KG

RAVENSBURG, , GM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-SEP-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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/s/

Ali Al-Hakim
12/2/04 02:56:02 PM
CHEMIST

Liang Zhou
12/2/04 03:11:39 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 20287/035
Org Code : 180
Priority : 1S

Sponsor: PHARMACIA AND UPJOHN
7171 PORTAGE RD
KALAMAZOO, MI 49001

Stamp Date : 17-MAR-2004
PDUFA Date : 17-JAN-2005
Action Goal :
District Goal: 13-DEC-2004

Brand Name : FRAGMIN
Estab. Name:
Generic Name: DALTEPARIN SODIUM
Dosage Form: (INJECTION)
Strength : 2500 & 5000 IU/.2ML

FDA Contacts: D. MOORE Project Manager (HFD-180) 301-827-7476

A. AL HAKIM Review Chemist (HFD-180) 301-827-7467

L. ZHOU Team Leader (HFD-180) 301-827-1251

Overall Recommendation: ACCEPTABLE on 01-NOV-2004by J. D AMBROGIO (HFD-322) 301-827-9049

ACCEPTABLE on 24-SEP-2004by S. ADAMS (HFD-322) 301-827-9051

Establishment: CFN : 9610708 FEI : 1000654629

PHARMACIA & UPJOHN COORDINATION CENTER

RIJKSWEG 12

PUURS, , BE

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-NOV-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment: CFN : 9610900 FEI : 3002270322

VETTER PHARMA FERTIGUNG GMBH AND CO KG

RAVENSBURG, , GM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-SEP-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

MEMORANDUM - STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	**20-287 SE1-035**
Drug Name:	Fragmin (dalteparin sodium) injection
Indication(s):	Extended treatment of symptomatic venous thromboembolism (VTE) to prevent VTE recurrence in cancer patients
Applicant:	Pfizer, Inc
Date(s):	Date of Submission: Electronic NDA dated March 16, 2004 NDA Supplement Amendment dated May 13, 2004 Various other supplements between 2005 & 2007
Review Priority:	Standard
Biometrics Division:	BIOMETRICS DIVISION V
Statistical Reviewer:	Satish C. Misra, Ph. D.
Concurring Reviewers:	STATISTICAL TEAM LEADER: Jyoti Zalkikar, Ph. D. DIRECTOR, BIOMETRICS DIVISION V Aloka Chakravarty, Ph. D.
Medical Division:	Division of Medical Imaging and Hematology Products
Clinical Team:	CLINICAL REVIEWER: Andrew Dmytrijuk, M.D..
Project Manager:	Diane V. Leaman

Keywords: NDA Review, Clinical Studies, Single study, missing data, Descriptive Statistics, Confidence Intervals

A. Background

Fragmin injection (dalteparin sodium injection) injection was approved for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction when concurrently administered with aspirin therapy.

Fragmin injection was also approved for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):

- in patients undergoing hip replacement surgery;
- in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- in medical patients who are risk for thromboembolic complication due to severely restricted mobility during acute illness.

In this NDA, the sponsor sought approval of Fragmin injection for extended treatment of symptomatic venous thromboembolism (VTE) to prevent recurrence in cancer patients.

On March 16, 2004, the sponsor submitted one pivotal Phase III study: CLOT (98-Frag-069) entitled "Randomized Comparison of Low Molecular Weight Heparin versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients with Venous Thromboembolism. The open-label, 677-patient CLOT study found that long-term dalteparin therapy significantly reduced recurrent venous thromboembolism (VTE) relative to oral anticoagulants (risk reduction 52%).

In the trial, Fragmin was administered via daily 200 I.U./kg subcutaneous injections for one month followed by daily 150 I.U./kg subcutaneous injections for five months. The majority of the benefit in VTE reduction in the treatment group occurred in the first month of therapy.

The statistical review and evaluation was performed by Milton Fan and documented in EDR (Electronic Document Room) on December 3, 2004.

The summary and recommendations are given below.

> "For extended treatment of symptomatic venous thromboembolism to prevent recurrence in cancer patients, Study 98-FRAG-069 showed dalteparin sodium was superior to oral anticoagulant in reducing the risk of recurrent symptomatic VTE. However, the results of subgroup analysis of number patients with first recurrent adjudicated-positive VTE revealed that the superiority of dalteparin over OAC (oral anticoagulant therapy using a coumarin derivative) was inconsistent among subgroups of country, type of tumor (solid vs. hematological), extent of tumor, and previous VTE. The dalteparin group was worse than OAC group for patients with hematological cancer, patients with non metastatic cancer, and patients with previous VTE. Furthermore, the treatment difference between two treatments for survival was not statistically significant.

The evidence of efficacy given in Study 98-FRAG-069 alone is not statistical persuasive. These efficacy results have not been replicated in another study."

In February 2006, further examination of the mortality data for the CLOT study by the medical review team during the current review cycle found that, although the time to death and overall mortality at the end of 6 months treatment and end of follow up (12 months) were similar in the two treatment groups, there appeared to be a higher rate of "on treatment " deaths in the dalteparin group as compared to the OAC group.

Some post-hoc analyses of the number of patients who were discontinued due to death, and "on treatment deaths" were performed by Milton Fan and documented in EDR (Electronic Document Room) on March 21, 2006, and Jyoti Zalkikar related to discussion of biases on May 1, 2006.

The results were presented to *Oncologic Drugs Advisory Committee* on September 26, 2006. The Oncologic Drugs Advisory Committee recommended approval of the low molecular weight heparin (***Fragmin***) for use in cancer patients.

Subsequently, sponsor submitted further information.

B. Summary of the Clinical Trial (CLOT study).

Patients with Cancer and Acute Symptomatic Venous Thromboembolism

In a prospective, multi-center, open-label, clinical trial, 676 patients with cancer and newly diagnosed, objectively confirmed acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were studied. Patients were randomized to either Fragmin 200 IU/kg (max 18,000 IU/ s.c. daily for one month) then 150 IU/kg (max 18,000 IU s.c. daily for five months (FRAGMIN arm) or FRAGMIN 200 IU/kg (max 18,000 IU s.c. daily for five to seven days and oral anticoagulant for six months (OAC arm). In the OAC arm, oral anticoagulation was adjusted to maintain an INR of 2 to 3. Patients were evaluated for recurrence of symptomatic venous thromboembolism (VTE) every two weeks for six months.

The median age of patients was 64 years (range: 22 to 89 years); 51.5% of patients were females; 95.3% of patients were Caucasians. Types of tumors were: breast (16%), lung (13.3%), gastrointestinal tract (23.7%), genito-urinary (21.5%), hematological tumors (10.4%) or other tumors (15.1%). Venous thrombotic events were adjudicated by a blinded central committee.

A total of 27 (8.0%) and 53 (15.7%) patients in the FRAGMIN and OAC arms, respectively, experienced at least one episode of a symptomatic DVT and/or PE during the 6-month study period. Most of the difference occurred during the first month of treatment (see Table 1). The benefit was maintained over the 6-month study period.

Table 1

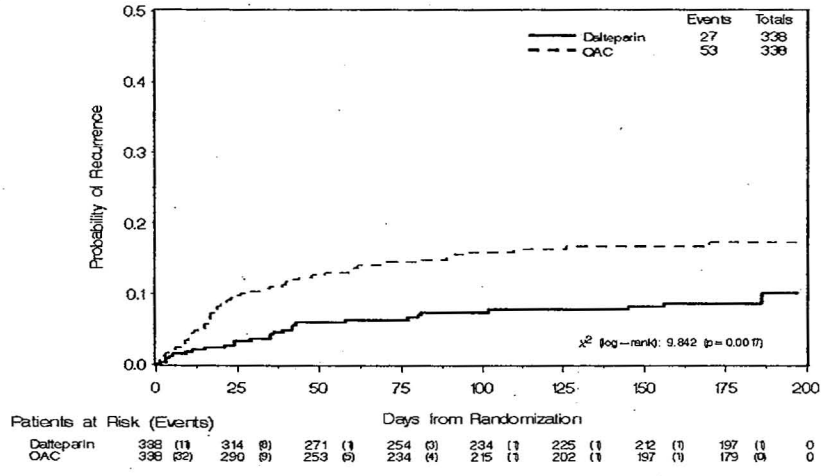
Recurrent VTE in Patients with Cancer (Intention to treat population)[1]

Study Period	FRAGMIN arm			OAC arm		
	FRAGMIN 200 IU/kg (max. 18,000 IU) s.c. once daily x 1 month, then 150 IU/kg (max. 18,000 IU) s.c. once daily x 5 months			FRAGMIN 200 IU/kg (max 18,000 IU) s.c. once daily x 5 to 7 days and OAC for 6 months (target INR 2 to 3)		
	Number at Risk	Patients with Venous Thromboembolism	%	Number at Risk	Patients with Venous Thromboembolism	%
Total	338	27	8.0	338	53	15.7
Week 1	338	5	1.5	338	8	2.4
Week 2-4	331	6	1.8	327	25	7.6
Weeks 5-28	307	16	5.2	284	20	7.0

[1] Three patients in the FRAGMIN group and 5 patients in the OAC arm experienced more than 1 VTE over the 6-month study period.

In the intent-to-treat population that included all randomized patients, the primary comparison of the cumulative probability of the first VTE recurrence over the 6-month study period was statistically significant (p=0.0017) in favor of the FRAGMIN arm, with most of the treatment difference evident in the first month. (see Figure 1).

Figure 1
Time to First Recurrent Adjudicated Positive VTE in Patients with Cancer During the 6-month Study Period



C. Indication and Usage : Proposed Revised Label

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

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

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

FRAGMIN is also indicated for the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer.

D. Summary and Conclusion:

The open-label, 677-patient 98-FRAG-069 (CLOT) study found that long-term dalteparin therapy significantly reduced recurrent venous thromboembolism (VTE) relative to oral anticoagulants (risk reduction 52%). Most of the benefit occurred during the first month of treatment. The benefit was maintained over the 6-month study period.

The mortality data and post-hoc analyses of the number of patients who were discontinued due to death, and "on treatment deaths" revealed that, although the time to death and overall mortality at the end of 6 months treatment and end of follow up (12 months) were similar in the two treatment groups, there appeared to be a higher rate of "on treatment " deaths in the dalteparin group as compared to the OAC group.

The Oncologic Drugs Advisory Committee unanimously recommended approval of the low molecular weight heparin (***Fragmin***) for use in cancer patients on September 26, 2006.

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/s/

Satish Misra
4/25/2007 03:16:16 PM
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Jyoti Zalkikar
4/25/2007 03:49:41 PM
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Aloka Chakravarty
4/25/2007 04:52:33 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review
Review for HFD 180

7-January-2005

NDA:	20-287/SE1-035(BC)
Drug Product Name	
Proprietary:	Fragmin®
Non-proprietary:	dalteprin sodium, injection
Drug Product Classification:	Standard
Review Number:	2
Subject of this Review	
Submission Date:	January 5, 2005
Receipt Date:	January 6, 2005
Consult Date:	January 7, 2005
Date Assigned for Review:	January 7, 2005
Submission History (for amendments only)	
Date(s) of Previous Submission(s):	September 20, 2004
Date(s) of Previous Micro Review(s):	January 4, 2005
Applicant/Sponsor	
Name:	Pfizer Inc.
Address:	235 E 42nd Street New York, NY 10017
Representative:	Ms. Ursula Browne
Telephone:	212-733-6354
Name of Reviewer:	Stephen E. Langille, Ph.D.
Conclusion:	Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: Prior approval

2. SUPPLEMENT PROVIDES FOR: (b) (4)

3. MANUFACTURING SITE: Vetter Pharma-Fertigung
Ravensburg, Germany

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Solution for injection
- Subcutaneous
- 10,000 IU, 12,000 IU, 15,000 IU and 18,000 IU

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment for symptomatic venous thromboembolism

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: Ursula Browne from Pfizer Regulatory Affairs was contacted by phone several times in December of 2004 regarding a Letter of Authorization for DMF (b) (4). In a January 5, 2005, letter to the Agency, Pfizer declined the option of using (b) (4) for Fragmin®.

filename: C:/Reviews/N020287S035R2.DOC

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
NDA 20-287/SEI-035 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -
Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
The applicant seeks approval for (b) (4)

B. Brief Description of Microbiology Deficiencies -
No deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies -
Not applicable

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Stephen E. Langille, Ph.D.
Supervisor/Team Leader

C. CC Block
In DFS

Product Quality Microbiology Assessment

The first review of NDA 20-287/SEI035(BC) was completed on January 4, 2005. The Applicant responded to the microbiological deficiency identified in the first review with a letter dated January 5, 2005. The microbiological deficiency is provided below in boldface type. A summary of the Applicant's response is provided in regular type.

The Applicant should provide the (b) (4) **The DMF referred to the in Letter of Authorization provided in December 15, 2004 did not contain any information regarding the** (b) (4)

The Applicant has withdrawn the option of using (b) (4) for Fragmin®. The Applicant will instead use (b) (4) according to validated and approved processes at the Vetter Pharma-Fertigung manufacturing facility.

Satisfactory

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/s/

Stephen Langille
1/7/05 11:52:26 AM
MICROBIOLOGIST

David Hussong
1/7/05 02:46:55 PM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD 180

4-January-2005

NDA:	20-287/SCM035
Drug Product Name	
Proprietary:	Fragmin®
Non-proprietary:	dalteprin sodium, injection
Drug Product Classification:	Standard
Review Number:	1
Subject of this Review	
Submission Date:	September 20, 2004
Receipt Date:	September 21, 2004
Consult Date:	September 22, 2004
Date Assigned for Review:	October 7, 2004
Submission History (for amendments only)	
Date(s) of Previous Submission(s):	Not applicable
Date(s) of Previous Micro Review(s):	Not applicable
Applicant/Sponsor	
Name:	Pfizer Inc.
Address:	235 E 42nd Street New York, NY 10017
Representative:	Ms. Ursula Browne
Telephone:	212-733-6354
Name of Reviewer:	Stephen E. Langille, Ph.D.
Conclusion:	Approvable pending revision

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: Prior approval

2. SUPPLEMENT PROVIDES FOR: [redacted] (b) (4)

3. MANUFACTURING SITE: Vetter Pharma-Fertigung
Ravensburg, Germany

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Solution for injection
- Subcutaneous
- 10,000 IU, 12,000 IU, 15,000 IU and 18,000 IU

5. METHOD(S) OF STERILIZATION: [redacted] (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment for symptomatic venous thromboembolism

B. SUPPORTING/RELATED DOCUMENTS: DMF [redacted] (b) (4)

C. REMARKS: Ursula Browne from Pfizer Regulatory Affairs was contacted by phone several times in December of 2004 regarding a Letter of Authorization for DMF [redacted] (b) (4)

filename: C:/Reviews/N020287S035R1.DOC

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
NDA 20-287/SEI-035 approval pending the resolution of product quality microbiology issues.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -
Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
The applicant seeks approval for (b) (4)

B. Brief Description of Microbiology Deficiencies -
The Applicant failed to provide adequate information regarding the (b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies -
Not applicable

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Stephen E. Langille, Ph.D.
Supervisor/Team Leader

C. CC Block
In DFS

4 Page(s) Withheld

___X___ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

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/s/

Stephen Langille
1/4/05 03:12:00 PM
MICROBIOLOGIST

David Hussong
1/4/05 04:20:45 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

NDA/Serial Number:	20-287/S-035
Drug Name:	Fragmin (dalteparin sodium) injection
Indication(s):	Extended treatment of symptomatic venous thromboemblism (VTE) to prevent VTE recurrence in cancer patients
Applicant:	Pfizer
Date(s):	NDA dated March 16, 2004
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Milton C. Fan, Ph.D. (HFD-715)
Concurring Reviewers:	Stella Grosser, Ph.D. (HFD-715)
Medical Division:	Gastrointestinal and Coagulant Drug Product (HFD-180)
Clinical Team:	Andrew Dmytrijuk, M.D. (HFD-180)
Project Manager:	Diane Moore (HFD-180)

Keywords: clinical study, single study, missing data, increasing sample size

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor has submitted one pivotal Phase III study: 98-FRAG-069 for the claim.

For extended treatment of symptomatic venous thromboembolism to prevent VTE recurrence in cancer patients, Study 98-FRAG-069 showed dalteparin sodium was superior to oral anticoagulant in reducing the risk of recurrent symptomatic VTE. However, the results of subgroup analysis of number patients with first recurrent adjudicated-positive VTE revealed that the superiority of dalteparin over OAC were inconsistent among subgroups of country, type of tumor (solid vs. hematological), type of tumor, extent of tumor, and previous VTE. The dalteparin group was worse than OAC group for patients with hematological cancer, patients with non metastatic cancer, and patients with previous VTE. Furthermore, the treatment difference between two treatments for survival was not statistically significant.

The evidence of efficacy given in Study 98-FRAG-069 alone is not statistical persuasive. These efficacy results have not been replicated in another study.

1.2 Brief Overview of Clinical Studies

1.2.1 Study 98-FRAG-069

This study was a multicenter (48 centers), multinational (8 countries), randomized, open label study comparing the efficacy and safety of the LWMH dalteparin sodium (Fragmin) versus oral anticoagulant therapy (OAT) using a coumarin derivative for long term anticoagulation in cancer patients with acute VTE.

The objective of this study was to compare the relative efficacy and safety of the LMWH dalteparin sodium (Fragmin) with those of anticoagulant therapy using a coumarin derivative for long term anticoagulation in cancer patients with acute VTE.

The primary objective was to compare symptomatic recurrent VTE between the two groups.

The secondary objectives were to compare the two groups in terms of: bleeding (both major and all bleeding); development of new, symptomatic DVT, PE or central venous thrombosis of the upper limb(s), neck or chest; survival; and general safety.

Inpatients or outpatients with active malignancy and with diagnosed acute, symptomatic proximal lower limb DVT, PE or both were enrolled. Proximal lower limb DVT was defined as the presence of thrombus in the popliteal or more proximal veins.

A 1:1 randomization to test drug or control arm occurred at the time of confirmed VTE diagnosis.

All patients received the full therapeutic doses of Fragmin 200 I.U./kg subcutaneously once daily for a minimum of five days as initial therapy.

For long-term treatment, patients randomized to test drug continued to receive Fragmin at the full therapeutic dose (200 I.U./kg, maximum 18,000 I.U.) for the first month and then received a reduced dose the remainder of 6-month study period. For the remainder of the 6-month study period, pre-filled syringes of Fragmin was supplied and the following weighted-based schedule using low doses (approximately 75% - 83% of the therapeutic dose) of Fragmin was used.

Fragmin for the initial period of treatment (minimum five days) in the control arm and for first month of treatment in the experimental group was provided as a solution of injection in multi-dose vials (25,000 I.U./mL).

Scheduled Dose Reduction of Fragmin at Month 1

Body Weight (kg)	Fragmin Dose (I.U.)	Dose Range (I.U./kg)	Mean Dose Reduction (%)
≤ 56	7,500	minimum 134	25
57 to 68	10,000	147 to 175	20
69 to 82	12,500	152 to 181	17
83 to 98	15,000	153 to 181	17
≥ 99	18,000	maximum 182	No reduction

This dose reduction was implemented to minimize bleeding while maintaining efficacy during the follow-up period.

For transient period of thrombocytopenia, study medication should be withheld if the platelet count dropped below 50 x 10^9/L and should be restarted when the platelet count recovered about 50 x 10^9/L. If the platelet count was between 50 and 100 x 10^9/L, then the dose of Fragmin should be reduced according the table given below and target INR should be lowered to 2.0 (range 1.5 to 2.5). Once the platelet count returned to greater than or equal to 100 x 10^9/L, the protocol Fragmin dose or target INR (2.5, range 2.0 to 3.0) should be resumed.

Initial one-month therapy: reduce dose to 150 I.U./kg once daily (25% dose reduction).
Long-term therapy: as per table below.

Fragmin Dose Reduction for Thrombocytopenia (50- 100 x 10^9/L)

Body Weight (kg)	Scheduled Fragmin Dose (I.U.)	Reduced Fragmin Dose (I.U.)	Mean Dose Reduction (%)
≤ 56	7,500	5,000	33
57 to 68	10,000	7,500	25
69 to 82	12,500	10,000	20
83 to 98	15,000	12,500	17
≥ 99	18,000	15,000	17

For patients who developed significant renal failure (creatinine greater than 3 x upper limit of normal). Fragmin should be continued but to ensure patient safety, the dose of Fragmin should be adjusted to maintain a therapeutic level at 1.01 I.U./mL (range 0.5 to 1.4 I.U./mL).

Patients allocated to the control arm began oral anticoagulant therapy with a coumarin derivative along with Fragmin as the initial therapy. After receiving Fragmin for a minimum of five days and once the INR had achieved the therapeutic target range of 2.0 to 3.0 for two consecutive days, patients in the control group continued with oral anticoagulant therapy alone for the remainder of the 6-month study period.

Patients were assessed at clinic visit at Day 7 to 10, Day 30/Month 1, Month 3 and Month 6 and each biweekly telephone assessment.

Reasons that a patient should discontinue study medication prior to the end of the six-month study period included:

1. Recurrence of VTE in the leg(s) or lung.
2. Development of central venous thrombosis (CVT) of the upper limb(s), neck or chest.
3. Bleeding necessitating permanent discontinuation of all anticoagulant therapy.

In addition to the above, a patient might permanently discontinue study medication prior to the 6-month study period if, in the opinion of the Investigator, it was medically necessary, or if it was the wish of the patient.

To minimize bias, the following strategies were used: a priori objective criteria for qualifying and outcome events, pre-specified symptom criteria for triggering investigators for suspected recurrence, a priori diagnostic algorithms for work-up of suspected VTE recurrence and suspected central venous thrombosis development, and blinded assessment of outcome events by a Central Adjudication Committee.

Primary efficacy outcome event was symptomatic recurrent VTE of the leg(s) or lung during the six-month study period.

Patients presenting with signs and symptoms suggestive of recurrent VTE were investigated according to the pre-specified diagnostic algorithms and diagnosed based on objective testing.

The secondary outcome events during the six-month study period were:

1. Bleeding (major and all bleeding).
2. New, symptomatic, objectively documented DVT, PE or CVT of the upper limb(s), neck, or chest.
3. Death

Overall mortality (all cause), death due to hemorrhage or recurrence of VTE was assessed in both treatment groups. Each death occurring during the six-month study period was classified as one of four categories: attributable to PE, attributable to hemorrhage, attributable to the underlying cancer, or due to other causes. Mortality was followed up to 12 months from the time of randomization.

1.3 Statistical Issues and Finding

The sponsor has submitted one pivotal Phase III study: 98-FRAG-069 for the claim.

The primary comparison of the cumulative probability of first VTE recurrence over the 6-month study period was statistically significant (2-sided log-rank test, p=0.0017). There was a significant reduction of 52% in the risk of VTE recurrence over 6 months in the dalteparin as the risk ratio of dalteparin to OAC was 0.48 (95% CI, 0.30-0.77, likelihood ratio test, p=0.0016).

When the time to first recurrence was analyzed separately for DVT and PE, the difference between treatment groups was statistically significant in favor of dalteparin for DVT recurrent (2-sided log-rank test, p=0.0008). The estimated probability of DVT recurrence at 6 months decreased from 0.128 in the OAC group to 0.049 in the dalteparin group.

For recurrent PE the difference between two treatments was not statistically significant (2-sided log-rank test, p=0.3409). The probability of PE recurrence at 6 months was 0.058 in OAC group and 0.043 in the dalteparin group.

For the composite endpoint of first recurrent DVT or PE or new CVT at 6 months, the estimated probability of first recurrent DVT or PE or new CVT at 6 months was reduced from 0.175 in the OAC group to 0.095 in the dalteparin group. The comparison of the cumulative probability of first DVT or PE or CVT recurrence over the 6-mont study period was statistically significant in favor of dalteparin treatment (2-sided log-rank test, p=0.0028).

The cumulative probability of death at both 6 and 12 months was similar in the two treatment groups. The comparison of cumulative probability of death over 6 and 12

months for the two treatment groups was not statistically significant (2-sided log-rank test, p=0.56 for 6 months and p=0.57 for 12 months).

However, the results of subgroup analysis of number patients with first recurrent adjudicated-positive VTE revealed that the superiority of dalteparin over OAC were inconsistent among subgroups of country, type of tumor (solid vs. hematological), type of tumor, extent of tumor, and previous VTE. The dalteparin group was worse than OAC group for patients with hematological cancer, patients with non metastatic cancer, and patients with previous VTE. Furthermore, the treatment difference between two treatments for survival was not statistically significant.

The evidence of efficacy given in Study 98-FRAG-069 alone is not statistical persuasive. These efficacy results have not been replicated in another study.

2. INTRODUCTION

2.1 **Overview**

Fragmin injection (dalteparin sodium injection) injection was approved for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction when concurrently administered with aspirin therapy.

Fragmin injection was also approved for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):

- in patients undergoing hip replacement surgery;
- in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- in medical patients who are risk for thromboembolic complication due to severely restricted mobility during acute illness.

In the current NDA, the sponsor seeks approval of Fragmin injection for extended treatment of symptomatic venous thromboembolism (VTE) to prevent recurrence in cancer patients.

2.2 **Data Sources**

The sponsor has submitted one pivotal Phase III study: CLOT (98-Frag-069) entitled "Randomized Comparison of Low Molecular Weight Heparin versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients with venous thromboembolism.

All data were submitted in electronic format to the EDR. The sponsor has also submitted NDA Supplement Amendment dated May 13, 2004

3. STATISTICAL EVALUATION

3.1 **Evaluation of Efficacy**

3.1.1 **Study 98-FRAG-069**

3.1.1.1 **Study Design**

This study was a multicenter (48 centers), multinational (8 countries), randomized, open label study comparing the efficacy and safety of the LWMH dalteparin sodium (Fragmin) versus oral anticoagulant therapy (OAT) using a coumarin derivative for long term anticoagulation in cancer patients with acute VTE.

The objective of this study was to compare the relative efficacy and safety of the LMWH dalteparin sodium (Fragmin) with those of anticoagulant therapy using a coumarin derivative for long term anticoagulation in cancer patients with acute VTE.

The primary objective was to compare symptomatic recurrent VTE between the two groups.

The secondary objectives were to compare the two groups in terms of : bleeding (both major and all bleeding); development of new, symptomatic DVT, PE or central venous thrombosis of the upper limb(s), neck or chest; survival; and general safety.

Inpatients or outpatients with active malignancy and with diagnosed acute, symptomatic proximal lower limb DVT, PE or both were enrolled. Proximal lower limb DVT was defined as the presence of thrombus in the popliteal or more proximal veins.

A 1:1 randomization to test drug or control arm occurred at the time of confirmed VTE diagnosis.

All patients received the full therapeutic doses of Fragmin 200 I.U./kg subcutaneously once daily for a minimum of five days as initial therapy.

For long-term treatment, patients randomized to test drug continued to receive Fragmin at the full therapeutic dose (200 I.U./kg, maximum 18,000 I.U.) for the first month and then received a reduced dose the remainder of 6-month study period. For the remainder of the 6-month study period, pre-filled syringes of Fragmin was supplied and the following weighted-based schedule using low doses (approximately 75% - 83% of the therapeutic dose) of Fragmin was used.

Fragmin for the initial period of treatment (minimum five days) in the control arm and for first month of treatment in the experimental group was provided as a solution of injection in multi-dose vials (25,000 I.U./mL).

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Body Weight (kg)	Fragmin Dose (I.U.)	Dose Range (I.U./kg)	Mean Dose Reduction (%)
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69 to 82	12,500	152 to 181	17
83 to 98	15,000	153 to 181	17
≥ 99	18,000	maximum 182	No reduction

This dose reduction was implemented to minimize bleeding while maintaining efficacy during the follow-up period.

For transient period of thrombocytopenia, study medication should be withheld if the platelet count dropped below 50 x 10^9/L and should be restarted when the platelet count recovered about 50 x 10^9/L. If the platelet count was between 50 and 100 x 10^9/L, then the dose of Fragmin should be reduced according the table given below and target INR should be lowered to 2.0 (range 1.5 to 2.5). Once the platelet count returned to greater than or equal to 100 x 10^9/L, the protocol Fragmin dose or target INR (2.5, range 2.0 to 3.0) should be resumed

Initial one-month therapy: reduce dose to 150 I.U./kg once daily (25% dose reduction). Long-term therapy: as per table below.

Fragmin Dose Reduction for Thrombocytopenia (50- 100 x 10^9/L)

Body Weight (kg)	Scheduled Fragmin Dose (I.U.)	Reduced Fragmin Dose (I.U.)	Mean Dose Reduction (%)
≤ 56	7,500	5,000	33
57 to 68	10,000	7,500	25
69 to 82	12,500	10,000	20
83 to 98	15,000	12,500	17
≥ 99	18,000	15,000	17

For patients who developed significant renal failure (creatinine greater than 3 x upper limit of normal). Fragmin should be continued but to ensure patient safety, the dose of Fragmin should be adjusted to maintain a therapeutic level at 1.01 I.U./mL (range 0.5 to 1.4 I.U./mL).

Patients allocated to the control arm began oral anticoagulant therapy with a coumarin derivative along with Fragmin as the initial therapy. After receiving Fragmin for a minimum of five days and once the INR had achieved the therapeutic target range of 2.0 to 3.0 for two consecutive days, patients in the control group continued with oral anticoagulant therapy alone for the remainder of the 6-month study period.

Patients were assessed at clinic visit at Day 7 to 10, Day 30/Month 1, Month 3 and Month 6 and each biweekly telephone assessment.

Reasons that a patient should discontinue study medication prior to the end of the six-month study period included:

1. Recurrence of VTE in the leg(s) or lung.
2. Development of central venous thrombosis of the upper limb(s), neck or chest.
3. Bleeding necessitating permanent discontinuation of all anticoagulant therapy.

In addition to the above, a patient might permanently discontinue study medication prior to the 6-month study period if, in the opinion of the Investigator, it was medically necessary, or if it was the wish of the patient.

To minimize bias, the following strategies were used: a priori objective criteria for qualifying and outcome events, pre-specified symptom criteria for triggering investigators for suspected recurrence, a priori diagnostic algorithms for work-up of suspected VTE recurrence and suspected central venous thrombosis development, and blinded assessment of outcome events by a Central Adjudication Committee.

Primary efficacy outcome event was symptomatic recurrent VTE of the leg(s) or lung during the six-month study period.

Patients presenting with signs and symptoms suggestive of recurrent VTE were investigated according to the pre-specified diagnostic algorithms and diagnosed based on objective testing.

The secondary outcome events during the six-month study period were:

1. Bleeding (major and all bleeding).
2. New, symptomatic, objectively documented DVT, PE or central venous thrombosis of the upper limb(s), neck, or chest.
3. Death

Overall mortality (all cause), death due to hemorrhage or recurrence of VTE was assessed in both treatment groups. Each death occurring during the six-month study period was classified as one of four categories: attributable to PE, attributable to hemorrhage, attributable to the underlying cancer, or due to other causes. Mortality was followed up to 12 months from the time of randomization.

3.1.1.2 **Sponsor's Analysis**

A total of 677 patients were randomized: 338 in dalteparin group and 339 in OAC group. Of the 677 patients randomized, 1 patient randomized to the OAC group (#707-004) did not provide informed consent and was therefore excluded from the study before receiving any treatment. No data for this patient were collected. Three further patients randomized

to the OAC group (#504-021, #801-012, and #801-013) did not receive any study drug; thus, the ITT population comprised 676 patients (338 in the dalteparin group and 338 in the OAC group), and the as-treated population comprised 673 patients (338 in the dalteparin group and 335 in the OAC group).

Among 673 as-treated patients, 343 patients completed the study (180 in the dalteparin group and 163 in the OAC group).

The main reason for discontinuation in both groups was death and the majority of these deaths were related to the patients' underlying cancer.

Two types of OAC were used in the study. Warfarin was used all countries except Spain and the Netherlands where acenocoumarol was used.

More patients receiving dalteparin than those receiving OAC had at least one modification or temporary interruption of dosing (41.7% vs. 31.9%). This difference was mainly due to the higher proportion of dalteparin patients who had their dosing modified due to patient's weight change (13.9% vs. 0.9%).

The frequency of patients receiving ≥80% of the planned treatment was 96.6% with dalteparin and 79.1% with OAC.

3.1.1.2.1 **Planned Analysis**

Two data sets were employed in the statistical analysis: the intention-to-treated (ITT) and the as-treated analysis sets. The ITT included all patients who were randomized. The ITT set was used for the primary efficacy outcome and for the secondary outcomes of death and central venous thrombosis of the upper limb(s), neck or chest. The patients were excluded from the as-treated (AT) analysis sets, if they had violated the inclusion or exclusion criteria or they did not received study drug. The AT set was used for the primary efficacy outcome as well as for all of secondary outcomes.

All analyses were based on the first occurrence of each of the primary and secondary outcome events during the six-month study period. All events were assessed by the Central Adjudication Committee in a blinded fashion.

The time-to-first-event of the primary outcome (recurrent VTE) and the secondary outcomes (major bleeding; overall bleeding; VTE or central venous thrombosis of the upper limb, neck or chest; and death) was described using the Kaplan-Meier method for each treatment group and were compared using the log rank test. Statistical significance was declared if the two-sided p-value for the test fell below 0.05.

A supporting analysis for the primary efficacy outcome of recurrent VTE employed the Cox proportional hazard regression model to assess the treatment effect adjusting for potential prognostic factors assessed at study entry (e.g. age, performance status, type of VTE, previous history of VTE, active cancer chemotherapy).

The expected six-month event rate for recurrent VTE is 20% for cancer patients treated with an oral anticoagulant. In order to detect a 50% relative rate reduction in the LMWH treatment group) with 85% power and a two-sided Type I error of 5%, and based on the log rank test and a 1:1 sampling ratio, at least 70 events overall would be needed. Therefore, 234 patients per group would need to be enrolled in this study. Since between 15% and 20% of patients are anticipated to withdraw or die during the six month post randomization, the sample size is adjusted upward to 293 patients per arm.

The provision was included for an upward adjustment of sample size after a minimum of 125 patients had been enrolled in each arm. The decision to increase the sample size was to be made by the Steering Committee after a blinded review of the total number of observed VTE recurrences.

Accordingly, the blinded review was performed in July 2000 after 260 patients had been enrolled, but the results were inclusive. A second evaluation was planned by the Steering Committee and was performed in January 2001.

A total of 436 patients were eligible for this analysis. Using an extrapolation of the current event rate, it was concluded that an increase in total sample size from 586 patients to 676 patients would like satisfy the 85% power requirement. The sponsor agreed with the Steering Committee to support this increase.

Amendment 5 (28 March 2001) reported the result of the second blind review of the overall recurrence rate and introduced a further sample size adjustment upward to 676 patients, in order to increase the probability of reaching the targeted number of primary events.

3.1.1.2.2 **Treatment Group Comparability**

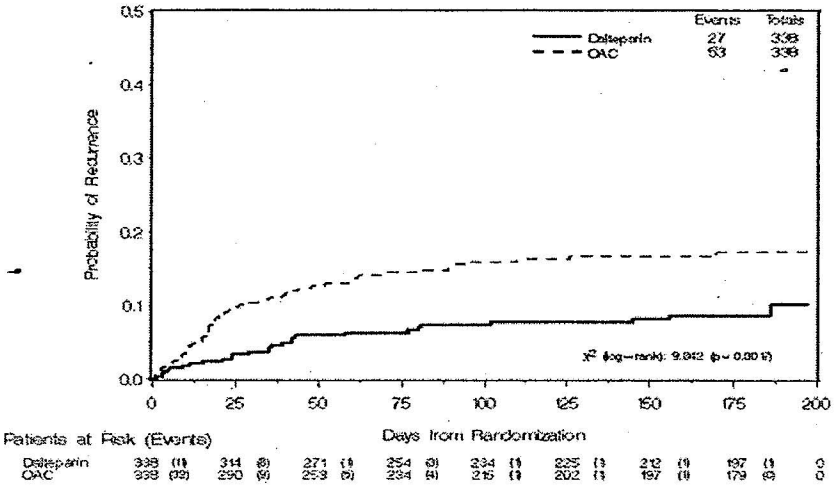
The summary of results of comparability of treatment groups at baseline for all randomized patients is given in Appendix Table 1.

As seem from Appendix Table 1, no significant differences between the two treatment groups were observed for demographic characteristics and baseline characteristics.

3.1.1.2.3 **Sponsor's Analysis of Primary Efficacy Parameter**

The primary efficacy endpoint in this study was the time to first VTE recurrence. The Kaplan-Meier curve for time to first recurrent adjudicated-positive VTE during the 6-month study period is given below.

Figure 1. Time to First Recurrent Adjudicated-positive VTE During the 6-month Study Period - Kaplan-Meier Curves (ITT Population)



A total of 27 of 338 patients randomized to dalteparin (8.0%) and 53 of 338 patients randomized to OAC (15.7%) experienced at least one adjudicated, symptomatic DVT and or PE during the 6-month study period. The primary comparison of the cumulative probability of first VTE recurrence over the 6-month study period was statistically significant (2-sided log-rank test, p=0.0017). There was a significant reduction of 52% in the risk of VTE recurrence over 6 months in the dalteparin as the risk ratio of dalteparin to OAC was 0.48 (95% CI, 0.30-0.77, likelihood ratio test, p=0.0016).

The secondary analysis for the as-treated population was consistent with the primary analysis.

3.1.1.2.3.1 Analysis of DVT and PE

The results of first VTE of first recurrence by type is given below.

Table 25. Type of First VTE Recurrence (ITT Population)

	Dalteparin N=338		OAC N=338	
Total VTE	**N**	**%**	**N**	**%**
DVT	14	4.1	37	10.9
PE	13	3.8	16	4.7
Nonfatal PE	8	2.4	9	2.7
Fatal PE	5	1.5	7	2.1

Abbreviations: DVT = deep vein thrombosis; OAC = oral anticoagulant; PE = pulmonary embolism; VTE = venous thromboembolic event

Source: Appendix 3.6.1

When the time to first recurrence was analyzed separately for DVT and PE, the difference between treatment groups was statistically significant in favor of dalteparin for DVT recurrent (2-sided log-rank test, p=0.0008). The estimated probability of DVT recurrence at 6 months decreased from 0.128 in the OAC group to 0.049 in the dalteparin group.

For recurrent PE the difference between two treatments was not statistically significant (2-sided log-rank test, p=0.3409). The probability of PE recurrence at 6 months was 0.058 in OAC group and 0.043 in the dalteparin group.

3.1.1.2.4 **Sponsor's Analysis of Secondary Efficacy Parameters**

The secondary efficacy endpoints were bleeding (major and all bleeding), new, symptomatic, objectively documented DVT, PE or central venous thrombosis of the upper limb(s), neck, or chest, and death during the six-month study period.

3.1.1.2.4.1 **Symptomatic Lower Limb DVT, PE, or CVT**

The summary of symptomatic lower limb DVT, PE or CVT is given below.

Table 30. Frequency of Adjudicated, Symptomatic Lower Limb DVT, PE, and CVT over 6 Months (ITT Population)

	Dalteparin N=338		OAC N=338	
	N	%	N	%
At least one event	29	8.6	54	16.0
Lower limb DVT	15	4.4	38	11.2
PE	10	3.0	11	3.3
Fatal PE	6	1.8	8	2.4
CVT	2	0.6	1	0.3

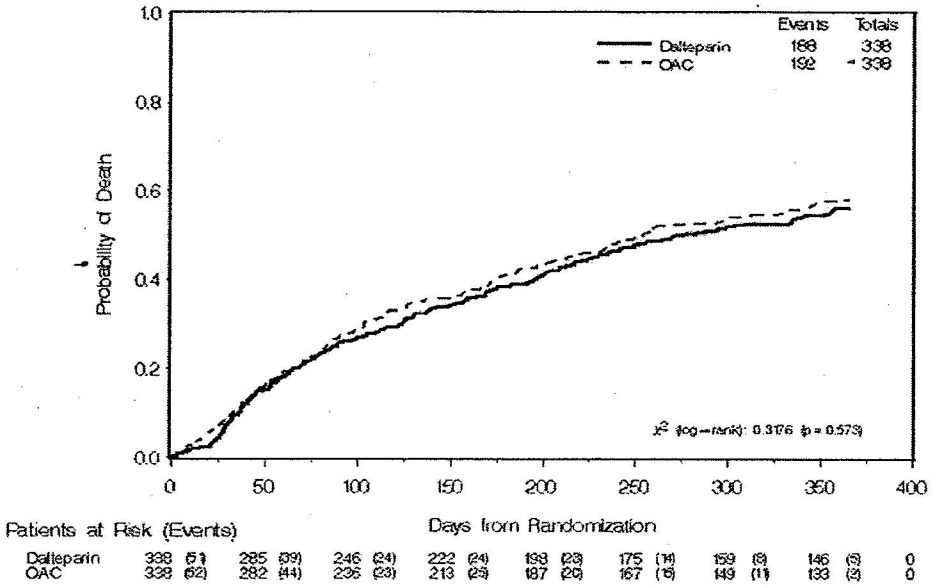
Abbreviations: CVT = central venous thrombosis; DVT = deep vein thrombosis; OAC = oral anticoagulant; PE = pulmonary embolism
Source: Table T7.1

For this composite endpoint, the estimated probability of first recurrent DVT or PE or new CVT at 6 months was reduced from 0.175 in the OAC group to 0.095 in the dalteparin group. The comparison of the cumulative probability of first DVT or PE or CVT recurrence over the 6-month study period was statistically significant in favor of dalteparin treatment (2-sided log-rank test, p=0.0028).

3.1.1.2.4.2 **Survival**

The Kaplan-Meier curves of time to death at 12 months are given below.

Figure 2. Time to Death During the 12 Months Following Randomization - Kaplan-Meier Curves (ITT Population)



There were a total of 131 and 137 deaths at 6 months in dalteparin and OAC groups, respectively; and 188 and 192 deaths within 12 months, respectively. The cumulative probability of death at both 6 and 12 months was similar in the two treatment groups. The comparison of cumulative probability of death over 6 and 12 months for the two treatment groups was not statistically significant (2-sided log-rank test, p=0.56 for 6 months and p=0.57 for 12 months).

3.1.1.3 **Reviewer' Comments and Evaluation**

3.1.1.3.1 **Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint**

3.1.1.3.1.1 **First VTE Recurrence**

The summary of the number and percentage of patients with first VTE recurrence is given below.

Number of Patients with First VTE Recurrence – - Protocol 98-FRAG-069

Intention to Treat Population
Protocol 98-FRAG-069

Dalteparin	OAC	Difference (dalt-oac)	p-value.
27/338 (8.0%)	53/338 (15.7%)	-7.7%	0.0027

Copied from Table 6
P-value was obtained using Fisher's exact test.

As seen from table above, the difference between treatment groups was statistically significant in favor of dalteparin for first VTE recurrence.

3.1.1.3.1.2 Subgroup Analysis

Subgroup analyses were preformed for number of patients with first recurrent adjudicated-positive VTE for the subgroups by country, age (aged <65 years vs. ≥65 years), gender, ECOG, and type of tumor for ITT population.

The results of subgroup analysis of number of patients with first recurrent adjudicated-positive VTE are given below.

Number of Patients with First Recurrent Adjudicated-positive VTE by Subgroup
ITT Population
Protocol 98-FRAG-069

Subgroup	Dalteparin	OAC	Difference	95% C. I.
Country				
Canada	10/126 (7.9%)	20/129 (15.5%)	-7.6%	(-15.4%, 0.3%)
US	3/58 (5.2%)	8/60 (13.3%)	-8.1%	(-18.5%, 2.2%)
United Kingdom	0/1 (0.0%)	0/1 (0.0%)	0.0%	
Italy	4/34 (11.8%)	4/33 (12.1%)	-0.4%	(-15.9%, 15.2%)
Australia	6/73 (8.2%)	17/71 (23.9%)	-15.7%	(-27.5%, -4.0%)
New Zealand	1/8 (12.5%)	1/8 (12.5%)	0.0%	(-32.4%, 32.4%)
The Netherlands	2/22 (9.1%)	2/19 (10.5%)	-1.4%	(-19.7%, 16.9%)
Spain	1/16 (6.3%)	1/17 (5.9%)	0.4%	(-15.9%, 16.7%)
Gender				
Male	15/159 (9.4%)	33/169 (19.5%)	-10.1%	(-17.6%, -2.6%)
Female	12/179 (6.7%)	20/169 (11.8%)	-5.1%	(-11.2%, 1.0%)
Age				
<65	18/182 (9.9%)	32/182 (17.6%)	-7.7%	(-14.7%, -0.7%)
≥65	9/156 (5.8%)	21/156 (13.5%)	-7.7%	(-14.2%, -1.2%)
ECOG				
0	7/80 (8.8%)	7/63 (11.1%)	-2.4%	(-12.3%, 7.6%)
1	8/135 (5.9%)	21/150 (14.0%)	-8.1%	(-14.9%, -1.2%)
2	12/118 (10.2%)	24/122 (19.7%)	-9.5%	(-18.4%, -0.6%)
3	0/5 (0%)	1/3 (33.3%)	-33.3%	(-86.7%, 20.0%)

Type of Tumor				
Solid	23/298 (7.7%)	53/308 (17.2%)	-9.5%	(-14.7%, -4.3%)
Hematological	4/40 (10%)	0/30 (0.0%)	10.0%	(0.7%, 19.3%)
Type of Tumor				
Breast	2/59 (3.4%)	2/49 (4.1%)	-0.7%	(-7.9%, 6.5%)
Gastrointestinal	7/79 (8.9%)	14/85 (16.5%)	-7.6%	(-17.7%, 2.5%)
Lung	5/40 (12.5%)	18/50 (36.0%)	-23.5%	(-40.3%, -6.7%)
Genito-urinary	4/77 (5.2%)	10/78 (12.8%)	-7.6%	(-16.6%, 1.3%)
Other	5/43 (11.6%)	9/46 (19.6%)	-7.9%	(-22.9%, 7.0%)
Hematological	4/40 (10.0%)	0/30 (0.0%)	10.0%	(0.7%, 19.3%)
Extent of Tumor				
Non Metastatic	7/115 (6.1%)	5/106 (4.7%)	1.4%	(-4.6%, 7.3%)
Metastatic	20/223 (9.0%)	48/232 (20.7%)	-11.7	(-18.1%, -5.3%)
Qualifying VTE				
DVT only	21/235 (8.9%)	38/230 (16.5%)	-7.6%	(-13.6%, -1.6%)
PE only	5/64 (7.8%)	8/65 (12.3%)	-4.5%	(-14.8%, 5.9%)
PE and DVT	1/39 (2.6%)	7/43 (16.3%)	-13.7%	(-25.8%, -1.6%)
Previous VTE				
Yes	3/35 (8.6%)	2/32 (6.3%)	2.3%	(-10.2%, 14.8%)
No	24/303 (7.9%)	51/306 (16.7%)	-8.7%	(-13.9%, -3.6%)
Prior Antineoplastic				
Yes	17/217 (7.8%)	28/194 (14.4%)	-6.6%	(-12.7%, -0.5%)
No	10/121 (8.3%)	25/144 (17.4%)	-9.1%	(-17.0%, -1.2%)
Prior Radiotherapy				
Yes	4/58 (6.9%)	10/56 (17.9%)	-11.0%	(-22.9%, 1.0%)
No	23/280 (8.2%)	43/282 (15.2%)	-7.0%	(-12.3%, -1.7%)
Prior Surgery				
Yes	2/37 (5.4%)	6/50 (12.0%)	-6.6%	(-18.2%, 5.0%)
No	25/301 (8.3%)	47/288 (16.3%)	-8.0%	(-13.3%, -2.7%)
Transient Risk Factors				
Yes	11/134 (8.2%)	15/136 (11.0%)	-2.8%	(-9.8%, 4.2%)
No	16/204 (7.8%)	38/202 (18.8%)	-11.0%	(-17.5%, -4.4%)

Compiled by this reviewer.

As seen from the table above, the results of superiority of dalteparin over OAC were inconsistent among subgroups of country, type of tumor (solid vs. hematological), type of tumor, extent of tumor, and previous VTE.

Furthermore, among eight countries, 95% confidence interval of treatment difference did not cover zero only for Australia. No treatment difference was observed in five countries (United Kingdom, New Zealand, Italy, the Netherlands, and Spain) with 24% of all

patients randomized. The total number of patients with first VTE recurrence for these five countries in dalteparin group was about the same as in OAC group.

There was treatment by type tumor interaction (p=0.0091, Breslow-Day test). The dalteparin group was worse than OAC group for patients with hematological cancer, with non metastatic, and with previous VTE.

3.1.1.3.2 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variables

3.1.1.3.2.1 First DVT only, Non-fatal PE, and Fatal PE

The summary of the number and percentage of patients with first DVT only, non-fatal PE, and fatal PE recurrence are given below.

Number of Patients with First DVT only, Non-fatal PE, and Fatal PE Recurrence
Intention to Treat Population
Protocol 98-FRAG-069

Patient with	Dalteparin	OAC	Difference (dalt – oca)	p-value
DVT only	14/338 (4.1%)	37/338 (10.9%)	-6.8%	0.0012
Non-fatal PE	8/338 (2.4%)	9/338 (2.7%)	-0.3%	1.0000
Fatal PE	5/338 (1.5%)	7/338 (2.1%)	-0.6%	0.7724

Copied from Table 25.
P-value was obtained by this reviewer using Fisher's exact test.

As seen from table above, the difference between treatment groups was statistically significant in favor of dalteparin for first DVT only recurrence. The treatment differences between two treatments for non-fatal PE and fatal PE recurrence were not statistically significant.

3.2 Evaluation of Safety

Slightly more dalteparin-treated than OAC-treated patients experienced at least one adjudicated major bleeding episode during the treatment (5.6% vs. 3.6%, respectively). Only 1 fatal bleeding event occurred during treatment in a lung cancer patient in the dalteparin group. Four dalteparin-treated and 3 OAC-treated patients developed major bleeding events in clinically critical sites. Ten dalteparin-treated (2.9%) and 5 OAC-treated patients (1.5%) permanently discontinued treatment due to a major hemorrhagic event.

A total of 22 and 13 major bleeding events occurred in dalteparin and OAC group, respectively. Three dalteparin patients and 1 OAC patient experienced more than one major hemorrhagic event during treatment.

During the acute treatment period (Week 1) the frequency of major bleeding events was comparable between the two treatment groups, while it increased during Weeks 2-5 in the patients treated with dalteparin.
Slightly more dalteparin-treated patients than OAC-treated patients reported at least one drug –related adverse event (35.9% vs. 31.7%, respectively).

Twenty-two patients (15 dalteparin, 7 OAC) were reported to have thrombocytopenia possibly related to study medication.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATION

4.1 Gender, Race and Age

No conclusion on race can be drawn due to lack of representation of Black and other races.

Subgroup analyses were preformed for the primary endpoint for the subgroups by age (aged <65 years vs. ≥65 years), and gender.

The results of subgroup analysis of primary efficacy endpoint are given below.

Number of Patients with First Recurrent Adjudicated-positive VTE by Subgroup
ITT Population
Protocol 98-FRAG-069

Subgroup	Dalteparin	OAC	Difference	95% C. I.
Gender				
Male	15/159 (9.4%)	33/169 (19.5%)	-10.1%	(-17.6%, -2.6%)
Female	12/179 (6.7%)	20/169 (11.8%)	-5.1%	(-11.2%, 1.0%)
Age				
<65	18/182 (9.9%)	32/182 (17.6%)	-7.7%	(-14.7%, -0.7%)
≥65	9/156 (5.8%)	21/156 (13.5%)	-7.7%	(-14.2%, -1.2%)

Compiled by this reviewer.
P-value was obtained using Fisher's exact test,

As seen from the table above, superiority of dalteparin sodium over placebo was consistent across subgroups of gender and age.

4.2 Other Special/Subgroup Population

Subgroup analyses were preformed for number of patients with first recurrent adjudicated-positive VTE for the subgroups by ECOG, and type of tumor, extent of tumor, qualifying VTE, previous VTE, prior antineoplastic, prior radiotherapy, prior surgery, and transient risk for ITT population.

The results of subgroup analysis of number of patients with first recurrent adjudicated-positive VTE are given below.

Number of Patients with First Recurrent Adjudicated-positive VTE by Subgroup
ITT Population
Protocol 98-FRAG-069

Subgroup	Dalteparin	OAC	Difference	95% C. I.
ECOG				
0	7/80 (8.8%)	7/63 (11.1%)	-2.4%	(-12.3%, 7.6%)
1	8/135 (5.9%)	21/150 (14.0%)	-8.1%	(-14.9%, -1.2%)
2	12/118 (10.2%)	24/122 (19.7%)	-9.5%	(-18.4%, -0.6%)
3	0/5 (0%)	1/3 (33.3%)	-33.3%	(-86.7%, 20.0%)
Type of Tumor				
Solid	23/298 (7.7%)	53/308 (17.2%)	-9.5%	(-14.7%, -4.3%)
Hematological	4/40 (10%)	0/30 (0.0%)	10.0%	(0.7%, 19.3%)
Type of Tumor				
Breast	2/59 (3.4%)	2/49 (4.1%)	-0.7%	(-7.9%, 6.5%)
Gastrointestinal	7/79 (8.9%)	14/85 (16.5%)	-7.6%	(-17.7%, 2.5%)
Lung	5/40 (12.5%)	18/50 (36.0%)	-23.5%	(-40.3%, -6.7%)
Genito-urinary	4/77 (5.2%)	10/78 (12.8%)	-7.6%	(-16.6%, 1.3%)
Other	5/43 (11.6%)	9/46 (19.6%)	-7.9%	(-22.9%, 7.0%)
Hematological	4/40 (10.0%)	0/30 (0.0%)	10.0%	(0.7%, 19.3%)
Extent of Tumor				
Non Metastatic	7/115 (6.1%)	5/106 (4.7%)	1.4%	(-4.6%, 7.3%)
Metastatic	20/223 (9.0%)	48/232 (20.7%)	-11.7	(-18.1%, -5.3%)
Qualifying VTE				
DVT only	21/235 (8.9%)	38/230 (16.5%)	-7.6%	(-13.6%, -1.6%)
PE only	5/64 (7.8%)	8/65 (12.3%)	-4.5%	(-14.8%, 5.9%)
PE and DVT	1/39 (2.6%)	7/43 (16.3%)	-13.7%	(-25.8%, -1.6%)
Previous VTE				
Yes	3/35 (8.6%)	2/32 (6.3%)	2.3%	(-10.2%, 14.8%)
No	24/303 (7.9%)	51/306 (16.7%)	-8.7%	(-13.9%, -3.6%)
Prior Antineoplastic				
Yes	17/217 (7.8%)	28/194 (14.4%)	-6.6%	(-12.7%, -0.5%)
No	10/121 (8.3%)	25/144 (17.4%)	-9.1%	(-17.0%, -1.2%)
Prior Radiotherapy				
Yes	4/58 (6.9%)	10/56 (17.9%)	-11.0%	(-22.9%, 1.0%)
No	23/280 (8.2%)	43/282 (15.2%)	-7.0%	(-12.3%, -1.7%)
Prior Surgery				
Yes	2/37 (5.4%)	6/50 (12.0%)	-6.6%	(-18.2%, 5.0%)
No	25/301 (8.3%)	47/288 (16.3%)	-8.0%	(-13.3%, -2.7%)
Transient Risk Factors				
Yes	11/134 (8.2%)	15/136 (11.0%)	-2.8%	(-9.8%, 4.2%)
No	16/204 (7.8%)	38/202 (18.8%)	-11.0%	(-17.5%, -4.4%)

Compiled by this reviewer.

As seen from the table above, the results of superiority of dalteparin over OAC were inconsistent among subgroups of type of tumor (solid vs. hematological), type of tumor, extent of tumor, and previous VTE.

There was treatment by type tumor interaction (p=0.0091, Breslow-Day test). The dalteparin group was worse than OAC group for patients with hematological cancer, with non metastatic, and with previous VTE.

5. SUMMARY AND CONCLUSIONS

5.1 **Statistical Issues and Collective Evidence**

The sponsor has submitted one pivotal Phase III study: 98-FRAG-069 for the claim.

The primary comparison of the cumulative probability of first VTE recurrence over the 6-month study period was statistically significant (2-sided log-rank test, p=0.0017). There was a significant reduction of 52% in the risk of VTE recurrence over 6 months in the dalteparin as the risk ratio of dalteparin to OAC was 0.48 (95% CI, 0.30-0.77, likelihood ratio test, p=0.0016).

When the time to first recurrence was analyzed separately for DVT and PE, the difference between treatment groups was statistically significant in favor of dalteparin for DVT recurrent (2-sided log-rank test, p=0.0008). The estimated probability of DVT recurrence at 6 months decreased from 0.128 in the OAC group to 0.049 in the dalteparin group.

For recurrent PE the difference between two treatments was not statistically significant (2-sided log-rank test, p=0.3409). The probability of PE recurrence at 6 months was 0.058 in OAC group and 0.043 in the dalteparin group.

For the composite endpoint of first recurrent DVT or PE or new CVT at 6 months, the estimated probability of first recurrent DVT or PE or new CVT at 6 months was reduced from 0.175 in the OAC group to 0.095 in the dalteparin group. The comparison of the cumulative probability of first DVT or PE or CVT recurrence over the 6-month study period was statistically significant in favor of dalteparin treatment (2-sided log-rank test, p=0.0028).

The cumulative probability of death at both 6 and 12 months was similar in the two treatment groups. The comparison of cumulative probability of death over 6 and 12 months for the two treatment groups was not statistically significant (2-sided log-rank test, p=0.56 for 6 months and p=0.57 for 12 months).

However, the results of subgroup analysis of number patients with first recurrent adjudicated-positive VTE revealed that the superiority of dalteparin over OAC were inconsistent among subgroups of country, type of tumor (solid vs. hematological), type of tumor, extent of tumor, and previous VTE. The dalteparin group was worse than OAC

group for patients with hematological cancer, patients with non metastatic cancer, and patients with previous VTE. Furthermore, the treatment difference between two treatments for survival was not statistically significant.

The evidence of efficacy given in Study 98-FRAG-069 alone is not statistical persuasive. These efficacy results have not been replicated in another study.

5.2 **Conclusion and Recommendations**

The sponsor has submitted one pivotal Phase III study: 98-FRAG-069 for the claim.

For extended treatment of symptomatic venous thromboembolism to prevent recurrence in cancer patients, Study 98-FRAG-069 showed dalteparin sodium was superior to oral anticoagulant in reducing the risk of recurrent symptomatic VTE. However, the results of subgroup analysis of number patients with first recurrent adjudicated-positive VTE revealed that the superiority of dalteparin over OAC were inconsistent among subgroups of country, type of tumor (solid vs. hematological), type of tumor, extent of tumor, and previous VTE. The dalteparin group was worse than OAC group for patients with hematological cancer, patients with non metastatic cancer, and patients with previous VTE. Furthermore, the treatment difference between two treatments for survival was not statistically significant.

The evidence of efficacy given in Study 98-FRAG-069 alone is not statistical persuasive. These efficacy results have not been replicated in another study.

6. Appendix

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 98-FRAG-069

ITT Population

Characteristics	Dalteparin (N=338)	OAC (N=338)	Between Treatment p-value
Sex			0.4416
Male	159 (47.0%)	169 (50.0%)	
Female	179 (53.0%)	169 (50.0%)	
Race			0.2278
N	337	338	
Caucasian	322 (95.5%)	322 (95.3%)	
Black	7 (2.1%)	8 (2.4%)	
Asian/Oriental	7 (2.1%)	3 (0.9%)	
Other Races	1 (0.3%)	5 (1.5%)	
Age (yr)			
Mean (SD)	62.3 (11.7)	63.2 (12.6)	0.3387
Age			1.0000
<65	182 (53.8%)	182 (53.8%)	
≥65	156 (46.2%)	156 (46.2%)	
Height (cm)			0.4907
N	331	328	
Mean (SD)	168.3 (9.7)	168.9 (12.1)	
Weight (kg)			0.3615
N	338	337	
Mean (SD)	73.6 (15.5)	74.7 (16.8)	
Performance Status (ECOG)			0.3371
0	80 (23.7%)	63 (18.6%)	
1	135 (39.9%)	150 (44.4%)	
2	118 (34.9%)	122 (36.1%)	
3	5 (1.5%)	3 (0.9%)	

Copied from Table 13.
P-values were computed by this reviewer.

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 98-FRAG-069 (Continued)

ITT Population

Characteristics	Dalteparin (N=338)	OAC (N=338)	Between Treatment p-value
Tumor Type			
N	336	337	
Solid Tumor			
Gastrointestinal	64 (18.9%)	68 (20.1%)	
Breast	59 (17.5%)	49 (14.5%)	
Lung	40 (11.8%)	50 (14.8%)	
Prostate	25 (7.4%)	22 (6.5%)	
Brain	14 (4.1%)	13 (3.8%)	
Cervix	14 (4.1%)	10 (3.0%)	
Pancreatic	12 (3.6%)	15 (4.5%)	
Uterus	13 (3.8%)	2 (0.6%)	
Ovary	11 (3.3%)	16 (4.7%)	
Bladder	10 (3.0%)	19 (5.6%)	
Testicle	1 (0.3%)	2 (0.6%)	
Other	33 (9.8%)	42 (12.4%)	
Hematological Tumor			
Non-Hodgkin's Lymphoma	22 (6.5%)	15 (4.4%)	
Hodgkin's Lymphoma	5 (1.5%)	2 (0.6%)	
Leukemia	8 (2.4%)	4 (1.2%)	
Multiple myeloma	4 (1.2%)	8 (2.4%)	
Solid Tumor Status			0.8442
No evidence of tumor	36 (12.1%)	33 (10.7%)	
Localized at primary site, no evidence of metastatic	39 (13.1%)	43 (14.0%)	
	223 (74.8%)	232 (75.3%)	
Hematological Tumor Status			0.7333
Not in Complete Remission	38 (95.0%)	29 (96.7%)	
Complete Remission	2 (5.0%)	1 (3.3%)	
Tumor Treatment (last 6 weeks)			
Antineoplastic Treatment	217 (64.2%)	194 (57.4%)	
Palliative Treatment	54 (16.0%)	50 (14.8%)	
Radiotherapy	58 (17.2%)	56 (16.6%)	
Surgery	37 (10.9%)	50 (14.8%)	
None	55 (16.3%)	64 (18.9%)	

Copied from Table 13.
P-values were computed by this reviewer.

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 98-FRAG-069 (Continued)

ITT Population

Characteristics	Dalteparin (N=338)	OAC (N=338)	Between Treatment p-value
Qualifying VTE			0.8796
DVT only	235 (69.5%)	230 (68.0%)	
PE only	64 (18.9%)	65 (19.2%)	
PE and DVT	39 (11.5%)	43 (12.7%)	
Previous VTE			
No VTE	299 (88.5%)	302 (89.3%)	
DVT only	21 (6.2%)	21 (6.2%)	
PE only	10 (3.0%)	7 (2.1%)	
PE and DVT	4 (1.2%)	4 (1.2%)	
Missing/Unknown	4 (1.2%)	4 (1.2%)	

Copied from Table 14.
P-values were computed by this reviewer.

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/s/

Milton Fan
12/2/04 05:22:37 PM
BIOMETRICS

Stella Grosser
12/3/04 02:45:02 PM
BIOMETRICS

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Clinical Biopharmaceutics Review

The Clinical Biopharmaceutics review was completed 11/29/04. No formal Clinical Biopharmaceutics review is needed for Cycle 3. One labeling comment was included in internal labeling discussions. The comment was in regard to the **DOSAGE AND ADMINISTRATION** section, **Dose reductions for renal insufficiency in extended treatment of acute symptomatic venous thromboembolism in patients with cancer** subsection. The term [redacted] (b) (4) should be replaced with the word "monitoring" in the sentence that reads "In patients with severely impaired renal function (CrCl < 30 mL/min), [redacted] (b) (4) monitoring for anti-Xa levels is recommended to determine the appropriate Fragmin dose."

Diane Leamon
4/23/07

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**

From: Tien-Mien Chen, Ph.D. (HFD-870)			To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE: 11/26/04	IND No.: Serial No.:	NDA No. 20-287 Supplement: SE1-035	DATE OF DOCUMENT **03/16/04**	
NAME OF DRUG **[Fragmin; dalteparin sodium]**	PRIORITY CONSIDERATION		Date of informal/Formal Consult: 04/20/04	
NAME OF THE SPONSOR: **[Pfizer]**				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☐ E-mail comments to: ☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ Formal Review/Memo (attached) ☒ • See comments below ☐ • See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☒ **NEED NOT BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

[X] Pfizer submitted Supplement SE1-035 to NDA 20-287 for Fragmin (dalteparin sodium) SC Injection. It contains a Phase III clinical trial to support the SC dosing of Fragmin in a new population, cancer patients, but no new human pharmacokinetic (PK) study was submitted.

No proposed revisions to the human PK section were made by the sponsor nor are new labeling changes made by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). Therefore, this supplement is acceptable from OCPB perspective and no further action is needed.

SIGNATURE OF REVIEWER: Tien-Mien Chen, Ph.D.	Date 11/26/04
SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.	Date 11/26/04
CC.: HFD # [180]; TL: [SD]	**Project Manager:** D. Moore **Date** 11/26/04

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

/s/

Tien-Mien Chen
11/29/04 09:33:33 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/29/04 03:26:04 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

OTHER REVIEW(S)

REGULATORY PROJECT MANAGEMENT LABELING
Division of Medical Imaging and Hematology Products (DMIHP)

Application Number: NDA 20-287/S-035 (Cycle 3)

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

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

Materials Reviewed: Package Insert (PI)
Immediate container labels

Submission Date: April 27, 2007
Receipt Date: April 20, 2007

Blister labeling
Carton labeling

Submission Date: April 30, 2007
Receipt Date: April 30, 2007

Background and Summary

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

On March 16, 2004 (received March 17, 2004) Pharmacia & Upjohn submitted Supplement-035 (S-035) to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The supplement was given an approvable action on January 14, 2005. Pharmacia & Upjohn resubmitted S-035 on September 14, 2005 (received September 16, 2005). The DMIHP sent Pharmacia & Upjohn a "Not Approvable" letter for this supplement on March 14, 2006. On February 28, 2007, received March 1, 2007, Pfizer Global Pharmaceuticals (agent for Pharmacia & Upjohn) resubmitted S-035. The RPM review of that labeling noted that the colors proposed for some of the new syringe presentations were similar to some of the existing colors for the already approved presentations. Specifically, the 2500 IU/0.2 mL, (sky blue) was similar to the 18,000 IU/0.72 mL (bright medium blue); the 5000 IU/0.2 mL (orange) was similar to the 12,500 IU/0.5 mL

(peach) and the 7500 IU/0.3 mL (light green) was similar to the 10,000 IU/0.4 mL (turquoise). A consult was sent to the Division of Medical Errors and Technical Support (DMETS) for comment. In a review dated April 12, 2007 by Jinhee Jahng, Pharm.D., DMETS, noted that "the colors for the proposed syringe strengths are similar to colors already used for existing syringe strengths. There is concern that the strengths with similar colors could easily be confused, leading to selection errors and resulting in the wrong dose being administered. We recommend that each syringe have a different, distinguishable color which may help practitioners differentiate between the Fragmin strengths, and thus reduce the potential for selection errors and potential overdose." In addition, the established name appears less prominent than the manufacturer name "Esai Inc." on the container labels. The font size and type of the manufacturer name competes with the prominence of the proprietary name, Fragmin. DMETS recommended that the sponsor decrease the prominence of the manufacturer name so that it appears less prominent than the proprietary and established names. Also the size and color of the font on the syringe blister backing is difficult to read and DMETS suggested that the sponsor consider using black font for the text and color blocking for the strength, similar to the presentation of the syringe strength on the container labels and carton labeling.

Labeling comments were sent to the sponsor in a regulatory letter on April 19, 2007. On April 26, 2007 (received April 27, 2007), Pfizer sent DMIHP revised PI labeling and revised immediate container labeling and a hard copy color guide with actual Pantone color chips for the Fragmin syringe presentations currently available commercially and the revised colors for the new syringe presentations associated with the oncology indication.

Review

I. Package Insert

The PI in S-035 (submitted April 27, 2007; received April 30, 2007) identified as "LAB-0058-8.12" Rev April 2007 was compared to the PI in the Agency letter dated April 19, 2007. The sponsor agreed with the proposed labeling revisions in the April 19, 2007 letter with the following exceptions:

A. **CLINICAL TRIALS** section:

1. In the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction subsection, in Table 1 entitled "efficacy of FRAGMIN in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction," the sponsor proposes to retain the heading "Dosing Regimen" to be consistent with Tables 2-6.

   Reviewer Comment: The proposal is editorial and acceptable

2. In the Patients with Cancer and Acute Symptomatic Venous Thromboembolism subsection, in the footnote to Table 7 entitled "Recurrent VTE in Patients with cancer (Intention to treat population)" the sponsor proposes to replace the term (b) (4) with

the term "arm" after the word "FRAGMIN" so that the foot note reads "Three patients in the FRAGMIN arm and 5 patients in the OAC arm experienced more than 1 VTE over the 6-month study period." The use of the term "arm" is consistent with the other references in the insert.

Reviewer Comment: The proposal is acceptable.

B. **WARNINGS** section, **Thrombocytopenia** subsection:

1. In the first paragraph, first sentence, the sponsor proposes to replace the word "in" with the word "supporting" and replace the word "populations" with the word "indication" so that the sentence reads "In FRAGMIN clinical trials supporting non-cancer indications, platelet counts of < 100,000/mm^3 and <50,000/mm^3 occurred in <1% and < 1% of patients, respectively." The sponsor claims that these studies included cancer patients so previous wording "non-cancer populations" was not accurate.

   Reviewer Comment: The proposed revision is acceptable.

2. In the second paragraph, in the first sentence that begins "In the clinical trial. . . " the sponsor proposes to replace the number '(b) (4) with the number '(b) (4)" after the phrase "occurred in" and to replace the number '(b) (4)" with the number "6.5%" after the phrase "occurred in" so that the sentence reads "In the clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated for up to 6 months in the Fragmin treatment arm, platelet counts of <100.000/mm^3 and >50,000/mm^3 occurred in (b) (4) % of patients, and platelet counts <50,000/mm^3 occurred in 6.5% of patients."

   Reviewer Comment: The Medical Officer suggests the following:
   In the clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated for up to 6 months in the Fragmin treatment arm platelet counts of <100,000/mm^3 occurred in 13.6% of patients, including 6.5% who also had platelet counts <50,000/mm^3." In addition, in the following sentence that begins "In the same . . ." the word (b) (4) should be deleted so that the sentence reads "In the same clinical trial, thrombocytopenia was reported as an adverse event in 10.9% of patients in the FRAGMIN arm and 8.1% of patients in the OAC arm."

C. **PRECAUTIONS section:**

Drug/Laboratory Test Interactions subsection, **Elevations of Serum Transaminases** sub-subsection:

In the first paragraph, first sentence reads (b) (4)

(b) (4)

The sponsor proposes to revise the sentence to read "In Fragmin clinical trials supporting non-cancer indications where hepatic transaminases were measured, asymptomatic increases in transaminase levels (SGOT/AST and AGPT/ALT) greater than three times the upper limit of normal of the laboratory reference range were seen in 4.7% and 4.2%, respectively, of patients during treatment with FRAGMIN."

The sponsor noted that the original Fragmin NDA studies resulted in 1.7% and 4.3% numbers. The larger studies conducted for the later indications results in the 4.7% and 4.2% numbers. The sponsor also noted that hepatic transaminases were not measured in all historic Fragmin studies. Percentage of patients with asymptomatic increases in transaminase levels were calculated using available data.

Reviewer Comment: The revised paragraph is acceptable.

D. **ADVERSE REACTIONS** section:

1. **Abdominal Surgery** subsection:

   In Table 11 entitled "**Bleeding Events in Medical Patients with Severely Restricted Mobility During Acute Illness**" the sponsor proposed to revise the number (b) (4) to "0.4%" and the number (b) (4) to "0.5%" in the Fragmin 5000 IU once daily s.c. n(5) column to be consistent with data presentations in other tables.

   Reviewer Comment: The revision is editorial and acceptable.

2. **Other** subsection:

   In the *Allergic Reactions* sub-subsection, the sponsor proposes to move the phrase "and skin necrosis" from the first sentence that begins "Allergic reactions . . ." and the second sentence that reads "A few cases of anaphylactoid reactions have been reported" from this section and move them to a new "*Post Marketing Experience*" sub-subsection. This section would now read: "Allergic reactions (ie., pruritus, rash, fever, injection site reaction, bulleous eruption) have occurred rarely."

   Reviewer Comment: The proposed revision is acceptable.

3. *Post Marketing Experience"* sub-subsection:

   The sponsor proposes a new *Post Marketing Experience* sub-subsection that contains the following three sentences:

   "Skin necrosis has occurred rarely. (b) (4) There have been isolated cases of alopecia reported that improved on drug discontinuation."

   Reviewer Comment: The sponsor provided data for this subsection in the April 27, 2007 submission. The data was not sufficient to support moving the anaphylactoid information to this subsection. The new subsection is acceptable. The sentence that reads "Skin necrosis has occurred rarely." is acceptable in this section. The two sentences that read "(b) (4) There have been isolated cases of alopecia reported that improved on drug discontinuation." should be kept in the ADVERSE REACTIONS section, Other subsection, Allergic Reactions sub-subsection.

E. **HOW SUPPLIED section:**

1. Following the storage conditions and the trademark comments, the sponsor revised the city, state and zip code address for Eaisi Inc. from "Teaneck, NJ 07666" to "Woodcliff Lake, NJ 07677."

   Reviewer Comment: The revision is editorial and acceptable.

2. The sponsor revised the identification number and revision date from LAB-0058-8.1 Revised December 2006" to "LAB-0058-8.2 Revised April 2007."

   Reviewer Comment: The revision is editorial and acceptable.

II. <u>Immediate container labeling</u>

Review Comment: The differences between computer monitors and printers when reading the pdf files containing the proposed syringe presentations made it difficult to distinguish the actual color of the syringe presentations. The colors were shared with Dr. Denise Toyer and Carol Holquist (DMETS) on April 30, 2007 for comment. (See attached e-mail). Upon comparison of the hard copy color guide with the actual Pantone color chips for the Fragmin syringe presentations, it is clear that the proposed colors for the syringes are sufficiently different to allow for easy distinguishing of each syringe presentation. The actual colors are clearer than the electronic pdf versions of the colors. The proposed colors for the syringe presentations both approved and proposed are acceptable.

III. Blister labeling

The sponsor has revised the blister labeling by using black font for the text and adding the respective color blocking for each strength syringe. The sponsor agrees to incorporate these revisions at the next printing.

Reviewer Comment: The revisions are consistent with the Agency recommendations in the April 19, 2007 information request letter. The proposed revisions to the blister labeling are acceptable.

IV. Carton Labeling

The sponsor has decreased the prominence of the company names and corporate logos on the carton labeling for revision at the next printing.

Reviewer Comment: The proposed revisions are in accordance with the recommendations in the April 19, 2007 Agency information request letter. The proposed revisions are acceptable.

Conclusions

1. The following items are editorial and acceptable: I.A.1., I.D.1., I.E.1.-2.

2. The following items are acceptable: I.A.2., I.B.1., I.C., I.D.2., II., III. and IV.

3. Item I. B.2. should be revised according to the recommendation stated above.

4. The new Postmarketing Experience subsection in I.D.3., with skin necrosis is acceptable. The allergic sentences noted in Item I.D.3. should be retained in the **ADVERSE REACTIONS** section, **Other** subsection, **Allergic Reactions** sub-subsection.

Note:

On April 30, 2007, Pfizer sent a telefacsimile to Diane Leaman, RPM with revisions to the PI. In that version, Pfizer made the previous revisions and the following additional revisions:

1. In the **Prophylaxis of Venous thromboembolism in Medical Patients with Severely Restricted Mobility During Acute Illness** subsection, the sponsor deleted the phrase "**Prophylaxis of Venous thromboembolism in**" so that the section reads: "**Medical Patients with Severely Restricted Mobility During Acute Illness. This is acceptable.**

2. In the **WARNINGS** section, **Thrombocytopenia** subsection, in the second paragraph, in the first sentence that begins "In the clinical trial. . . " the sponsor replaced the number

(b) (4)

" so that the sentence reads "In the clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated for up to 6 months in the Fragmin treatment arm platelet counts of <100,000/mm^3 occurred in 13.6% of patients, including 6.5% who also had platelet counts <50,000/mm^3." **This is acceptable.**

3. In the **WARNINGS** section, **Thrombocytopenia** subsection, in the second paragraph, in the second sentence that begins "In the same . . ." the word (b) (4) was deleted so that the sentence reads "In the same clinical trial, thrombocytopenia was reported as an adverse event in 10.9% of patients in the FRAGMIN arm and 8.1% of patients in the OAC arm." **This is acceptable.**

Diane Leaman, B.S.
Regulatory Health Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Kyong (Kaye) Kang
Chief, Project Management Staff
Division of Medical Imaging and
Hematology Products
Center for Drug Evaluation and Research

Andrew Dmytrijuk, M.D.
Medical Officer
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Kathy Robie-Suh, M.D., Ph.D.
Hematology Team Leader
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Attachment:

Diane,

Thanks for bringing the samples to us. As discussed the colors are better differentiated than previously presented. Therefore, DMETS has no further comments.

Denise.

-----Original Message-----
From: Leaman, Diane V
Sent: Monday, April 30, 2007 10:18 AM
To: Toyer, Denise P
Subject: FW: Fragmin colors

Denise,

I received a color palate for the Fragmin colors and it has definitive separate colors for all the Fragmin syringe presentations. I only have one copy and it is being archived. I made a copy that I can show you for concurrence for the Fragmin colors. Let me know if you would like to see it.

Diane Leaman
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Phone 301 796-1424

-----Original Message-----
From: Jahng, Jinhee
Sent: Monday, April 30, 2007 10:15 AM
To: Leaman, Diane V
Subject: Out of Office AutoReply: Fragmin colors

I will be out of the office starting April 30, 2007 and will return on Monday, May 7, 2007. If you need immediate assistance, please contact Denise Toyer at (301) 796-0549.

Thanks,
Jinhee

Drafted: dl/April 30, 2007
Initialed: K.Kang. A. Dmytrijuk, K.Robie-Suh 4.30.07
Finalized: May 1, 2007
Filename: N20287S035RPMLblrevCycle3.doc

RPM LABELING REVIEW

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

/s/

Diane V Leaman
5/1/2007 12:48:32 PM
CSO

Kyong Kang
5/1/2007 02:14:01 PM
CSO

Andrew Dmytrijuk
5/1/2007 03:14:39 PM
MEDICAL OFFICER

Kathy Robie-Suh
5/1/2007 03:37:24 PM
MEDICAL OFFICER

DIVISION DIRECTOR'S REVIEW MEMORANDUM FOR SUPPLEMENT
NEW INDICATION: Updated to Cite Prior Review

NDA:	20-287/SE1-035 (this is a third cycle review)
DRUG:	Dalteparin sodium injection
TRADE NAME:	Fragmin®
FORMULATION:	Prefilled syringes (multiple sizes) and multidose vials with specified Fragmin contents in (b) (4); the multidose vial also contains a specified content of benzyl alcoho (b) (4) single-use vials, containing (b) (4).
ROUTE:	Subcutaneous
DOSE:	For this new indication in cancer patients: 200 IU/kg once daily for a month followed by 150 IU/kg once daily for five months (maximum dose 18,000 IU daily)
SPONSOR:	Pfizer, Inc.
SUBMITTED:	February 28, 2007
PDUFA DUE DATE:	April 30, 2007
DD MEMO COMPLETED:	April 30, 2007
DD MEMO PREPARER:	Dwaine Rieves, MD, Acting Division Director Division of Medical Imaging and Hematology Products

SPONSOR'S PROPOSED NEW INDICATION:

"Fragmin is also indicated for the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer."

This updated memorandum is provided to clarify the prior reviews and inspections.

RELATED DRUGS:

Fragmin is the first FDA-approval of an anticoagulant as treatment for VTE specifically among patients with cancer. Multiple other anticoagulants are approved for VTE treatment among the broad population of patients.

RELATED REVIEWS:

Clinical:	Andrew Dmytrijuk, M.D.; Kathy Robie Suh, M.D., Ph.D.
Statistics:	Milton Fan, Ph.D, Jyoti Zalkikar, Ph.D.
Chemistry:	None for this third cycle--currently approved. A CMC review was performed by Ali Al-Hakim, Ph.D. for the first cycle.
Pharm-toxicology:	None--not applicable.
Microbiology:	None in third cycle; Stephen Langille, Ph.D in first cycle.
Clin Pharmacology:	None--not applicable.
DMETS:	Jinhee Jahng, Pharm.D
Advisory Committee:	Oncologic Drugs Advisory Committee on September 6, 2006 with a unanimous recommendation for approval.

RECOMMENDED REGULATORY ACTIONS:

1) Approval of the supplement for the proposed indication:

VTE is a relatively common complication among patients with cancer. Fragmin has been used for many years as an anticoagulant in the primary prevention of VTE. The indication proposed in this supplement was for the secondary prevention (or "treatment") of VTE among cancer patients.

The sponsor's clinical data, as outlined below, raised multiple concerns during the two review cycles. These issues were ultimately brought to an advisory committee where the data were fully vetted and the committee unanimously regarded the sponsor's data as robust evidence of the safety and efficacy of Fragmin for the new indication. The feedback from the committee provided an objective, informative perspective (approval) to which the review teams, in this third cycle, agree.

This supplement also approves four new presentations (strengths of prefilled syringes), an approval applicable to the higher dosages needed for the new indication.

2) Requirement of the sponsor to conduct post-marketing studies and to submit additional information:

Pfizer has agreed to two post-marketing clinical studies:

-to evaluate efficacy and safety of Fragmin in pediatric cancer patients (all ages). The final study report is to be submitted within 36 months of the approval.

-to evaluate the safety and efficacy of Fragmin in cancer patients (both metastatic and non-metastatic) receiving extended treatment with Fragmin for more than six months. The final study report is to be submitted within 60 months of the approval.

3) Compliance with Pediatric Research Equity Act (PREA) of 2003 expectations:

Pfizer has agreed to conduct a clinical study among pediatric cancer patients to support the usage in this population. This action maintains compliance with PREA.

REVIEW COMPONENTS:

Background

Fragmin is a low molecular weight heparin drug currently approved for VTE thromboprophylaxis in multiple settings (hip replacement, abdominal surgery, general medical illness among patients with restricted mobility) and also prophylaxis of ischemic complications in patients with unstable angina and non-Q wave myocardial infarction.

The sponsor conducted a single clinical study to support the proposed indication for use of Fragmin among cancer patients with VTE. Several aspects of this proposal raised special concerns for the clinical review team. Specifically:

- -the provision of data from a single study raised questions about the robustness of the data to support the approval
- - nearly half the patients died by the end of the study (supposedly due to cancer) and this high death rate added to concern about data robustness (as did certain subset analyses)

-the competing risk of death with recurrent VTE (the study's primary endpoint) made interpretation of the data difficult.

The many concerns regarding the sufficiency of the single study supporting the new indication resulted in FDA completing two full review of the data and issuing two action letters (first an "approvable" letter and secondly a "non-approvable" letter). Both action letters requested additional clinical studies to bolster the persuasiveness of the data. Because of the complex nature of the concerns regarding interpretation of the study's primary endpoint due to competing risks and accumulating post-marketing data that did not suggest new safety concerns for Fragmin (in the approved indications), the supplement was reviewed in detail at a September 6, 2006 ODAC meeting. The complex statistical issues were fully vetted and the committee unanimously recommended approval. This action was based upon inference of Fragmin's activity (based upon extensive experience for use of the product in the primary prevention of VTE) as well as the sponsor's single clinical study data (which were assessed as robust).

The current (third cycle) submission consists of revised product labeling and a commitment for post-marketing clinical studies.

Brief Regulatory Timeline

- Original Fragmin approval: December 22, 1994
- Submission of NDA supplement: March 16, 2004
- Approvable letter issued (first cycle): January 15, 2005
- Resubmission of NDA supplement: September 14, 2005
- Non-approvable letter issued (second cycle): March 15, 2006
- Advisory Committee: September 6, 2006
- Resubmission of NDA supplement: February 28, 2007
- PDUFA action (third cycle)/approval: April 30, 2007

Clinical Review

The clinical review was performed by Dr. Andrew Dmytrijuk (second and third cycle) and Dr. George Shashaty (first cycle). Dr. Kathy Robie Suh provided Team Leader expertise to the reviews and also provided secondary reviews. Dr. Milton Fan performed the statistical review (during initial cycles). I have examined the clinical and statistical reviews and I concur with the ultimate findings, comments and recommendations. I also concur with findings from other review disciplines from prior cycles (CMC, Clin pharm). These disciplines had minimal comments regarding the supplement.

Substantial evidence of safety and effectiveness for Fragmin usage in the new indication is derived from a single clinical study called the CLOT study. This study was an open label study conducted among 676 patients with cancer who also had a VTE. The patient population included patients with a broad array of underlying cancers (predominantly lung, breast) although non-solid cancer accounted for only 10% of the population.

The subjects were randomized (1:1) to either an "OAC" group or a "Fragmin" group. The OAC group received 200 IU/kg Fragmin once daily for 5 - 7 concurrent with oral anticoagulant (OAC, to INR of 2 - 3) followed by OAC alone for a total of six months.

The Fragmin group received Fragmin at 200 IU/kg once daily for a month followed by five months of Fragmin at 150 IU/kg once daily. The study terminated at the six month time point.

The primary endpoint was a time to event comparison of the occurence of symptomatic recurrent VTE. VTE recurrence was determined by an independent, central committee blinded to treatment assignment.

By the end of the study, approximately half the patients had died (with similar death rates between the two study groups). More deaths were the "cause" for study drug discontinuation in the Fragmin group. However, this aspect of drug discontinuation was discussed extensively at the advisory committee and the committee felt very strongly that this "study drug discontinuation" imbalance due to death was related to the open label nature of the study (where physicians would continue an injectable drug but would discontinue an oral drug due to the patient's debilitation). The committee's decision was bolstered by the intention-to-treat analysis that showed overall mortality rates were similar between the study groups.

The study's primary endpoint should a marked treatment effect (log rank p of 0.002) in favor of patient's receiving Fragmin. Overall, 8% of the Fragmin patients had a VTE recurrence while 16% of the OAC group had a VTE recurrence.

The major safety findings from the study related to modestly higher rates of major bleeding, thrombocytopenia and liver enzyme elevations in the Fragmin group. Overall, major bleeding events occurred in 6% Fragmin patients and 4% OAC patients. Thrombocytopenia adverse events occurred in 11% Fragmin patients and 8% OAC patients. Liver ALT elevations (any severity) occurred in 40% Fragmin patients and 31% OAC patients. Grade 3 (or higher) adverse event rates were much lower for these outcomes but were modestly higher in the Fragmin group.

Division of Scientific Investigation (DSI)

No inspection was performed in the third cycle. One clinical site was inspected during the first cycle review and no notable deficiencies were detected.

Financial Disclosure

As noted in Dr. Dmytrijuk's review, the sponsor has submitted required financial disclosure information and the information is acceptable.

Consultations

The DMETS consultants recommended revisions of the syringe container/carton labels to lessen the risk for medication errors. These modifications were performed by the sponsor.

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/s/

Rafel Rieves
4/29/2007 09:33:41 AM
MEDICAL OFFICER
This memo is updated to cite the reviews done in the prior cycle--specifically the inspection of a clinical site.

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Rafel Dwaine Rieves, M.D.
Acting Director, Division of Medical Imaging and Hematology Products

Through: Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

From: Jinhee L. Jahng, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support

Date: April 4, 2007

Re: OSE Review # 2007-760
Fragmin (dalteparin sodium injection)
10,000 IU (anti-factor Xa)/0.4 mL
12,500 IU (anti-factor Xa)/0.5 mL
15,000 IU (anti-factor Xa)/0.6 mL
18,000 IU (anti-factor Xa)/0.72 mL
NDA # 20-287/S-035

This memorandum is in response to an April 2, 2007 request from your Division for re-assessment of the container labels, carton, and insert labeling for Fragmin. Specifically, the Division has requested that DMETS review the four new syringe strengths [10,000 IU (anti-factor Xa)/0.4 mL, 12,500 IU (anti-factor Xa)/0.5 mL, 15,000 IU (anti-factor Xa)/0.6 mL, and 18,000 IU (anti-factor Xa)/ 0.72 mL] in support of the efficacy supplement (S-035) for the additional indication of extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The labels and labeling were previously reviewed in ODS Consult #05-0143-1 (March 3, 2006). It appears that the container labels and carton labeling remain the same since our last review; however, the insert labeling has revisions.

DMETS conducted a search of the FDA Adverse Event Reporting System (AERS) for any post-marketing safety reports of medication errors associated with Fragmin since our last review dated March 3, 2006. The MedDRA High Level Group Term (HLGT) "Medication Error", tradename, established name, and verbatim "Fragmin%" and "Dalteparin%" were used to perform the searches. This search did not reveal any new errors involving confusion with the nomenclature, labels, and labeling of Fragmin. The Drug Quality and Reporting System (DQRS) database was also searched for similar medication error reports. No new errors were retrieved.

In the re-review of the container labels, carton and insert labeling of Fragmin DMETS has focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement, which might minimize user error. Additionally, for your convenience, we have incorporated the comments made in our last review into this one.

A. GENERAL COMMENTS

DMETS notes that the colors for the proposed syringe strengths are similar to colors already used for existing syringe strengths. There is concern that the strengths with similar colors could easily be confused, leading to selection errors and resulting in the wrong dose being administered. We recommend that each syringe have a different, distinguishable color which may help practitioners

differentiate between the Fragmin strengths, and thus reduce the potential for selection errors and potential overdose.



B. CONTAINER LABELS

1. The established name appears less prominent than the manufacturer name, "Esai Inc". Additionally, the font size and type (bold) of the manufacturer name competes with the prominence of the proprietary name, Fragmin. Decrease the prominence of the manufacturer name so that it appears less prominent than the proprietary and established names.

2. The size and color of the font on the syringe blister backing is difficult to read (see labels on page 3. In particular, the yellow green, light blue, orange, and purple colors are the most difficult to read. Revise the colors to improve readability or increase the font size and prominence accordingly. The Sponsor may also wish to consider using black font for the text and using color blocking for the strength, similar to the presentation of the syringe strength on the container labels and carton labeling.

(b) (4)

C. CARTON LABELING

1. See GENERAL COMMENTS.

2. The company name and corporate logo appear to be occupying more than 1/3 of the label. Decrease the size of the name and logos so that it has less prominence than the proprietary and established names.

D. INSERT LABELING

1. We note a typographical error in Table 1 on page 3 of the insert labeling. Specifically, the Fragmin Dosing Regimen heading should read 120 IU/kg **q** 12hr s.c. (emphasis added). The "q" was omitted in the draft insert labeling. However, we recommend avoiding the use of all abbreviations in the labels and labeling since they are often misread and may lead to medication errors (i.e., "q", "s.c.", "qd", "bid", etc.). The "q" should be revised to read "every". As evidenced by our post-marketing surveillance, abbreviations and acronyms may be misinterpreted. We note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2006 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must 'Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization'. The abbreviation "q.d." is specifically listed as a dangerous abbreviation, acronym or symbol. Additionally, the Institute for Safe Medication Practices also publishes an "ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations" in which they also recommend avoiding the use of the abbreviation "q.d." Postmarketing experience has shown that "q.d." (once daily) may be confused with "q.i.d." (four times daily), especially if the period after the letter "q" or the tail of the letter "q" is misinterpreted as the letter "i". Revise accordingly (i.e., "q" to ready "every", "qd" to read "daily", "bid" to read "twice daily", "s.c." to read "subcutaneously", etc.).

2. We note the use of a terminal zeroes throughout the package insert labeling. We recommend that you avoid the use of terminal zeroes for expressions of numbers in all labels and labeling (i.e., 1 mL and not 1.0 mL) since it may result in misinterpretation of the number if the decimal point is not noticed. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs....the quantity of active ingredient when expressed in whole numbers shall be shown WITHOUT a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as the Institute for Safe Medication Practices list terminal zeroes on their dangerous abbreviations and dose designations list.

3. We recommend you change the heading of the MISCELLANEOUS sub-section in the WARNINGS section, to more accurately reflect the recommendation that the Fragmin multi-dose vials, preserved with benzyl alcohol, should not be used in pregnant women. The MISCELLANEOUS heading is non-specific as to the content of the section, and is easy for the reader to overlook. However, we also note that in a proposed version of the insert labeling (S-035), the warning has been changed from

the wording that Fragmin "should not be used in pregnant women" to "should be used with caution in pregnant women." The section now reads:

> *Each 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 be used with caution in pregnant women (see PRECAUTIONS, Pregnancy Category B, Nonteratogenic Effects).*

DMETS cannot comment on the clinical significance of using the Fragmin multi-dose vial with benzyl alcohol in pregnant women, but regardless of the strength of the warning used, the heading should more accurately reflect the contents of the warning in the section.

4. We note that the sponsor has included the concentration as headings for the individual strengths in the HOW SUPPLIED section (see below). However, the concentrations are absent on the actual container labels and labeling and we are concerned that this might introduce confusion and subsequent error because some of the concentrations and strengths overlap (i.e. 10,000IU/1 mL vs. 10,000 IU/0.4 mL and 12,500 IU/1 mL vs. 12,500 IU/0.5 mL). Similarly, we note that two multiple dose vial coexist, the 95,000 IU/9.5 mL vial and 95,000 IU/3.8 mL vial and we wonder whether having the concentration listed will introduce confusion.

We recommend deleting the headings and grouping the strengths in a numerical fashion, either in descending or ascending order.

(b) (4)



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/s/

Jinhee Jahng
4/12/2007 02:22:05 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/12/2007 02:32:20 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/12/2007 04:10:24 PM
DRUG SAFETY OFFICE REVIEWER

We recommend implementation of the above label and labeling recommendations. Please copy DMETS any correspondence forwarded to the sponsor pertaining to this issue. If you have any other questions or need clarification, please contact the OSE Project Manager, Samuel Chan, at 301-796-2283.

REGULATORY PROJECT MANAGEMENT LABELING
Division of Medical Imaging and Hematology Products (DMIHP)

Application Number: NDA 20-287/S-035 (Cycle 3)

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

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

Materials Reviewed: Package Insert (PI)
- Immediate container labels
- Blister labeling
- Carton labeling

Submission Date: February 28, 2007
Receipt Date: March 1, 2007

Background and Summary

Fragmin is a low molecular weight heparin (LMWH) product. The 2500 IU strength was approved December 22, 1994, for use in the prophylaxis of deep venous thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery, who are at risk of thromboembolic complications. The 5,000 IU dosage form was approved March 18, 1996, for prevention of DVT in patients at high risk. Fragmin was approved for prophylaxis of DVT which may lead to PE in patients undergoing hip replacement surgery on March 30, 1999. Fragmin was approved for treatment of unstable angina and non-Q-wave myocardial infarction for the prevention of ischemic complications in patients on concurrent aspirin therapy on May 25, 1999. The 10,000 IU syringe was approved November 14, 2000.

Pfizer Global Pharmaceuticals (Pfizer) merged with Pharmacia and Upjohn on April 14, 2003. Pharmacia and Upjohn remains the sponsor of NDA 20-287. Pfizer is the authorized agent for Pharmacia and Upjohn for this NDA.

Pfizer submitted annual report Y-011 on February 28, 2006 (received March 1, 2006). The labeling in Y-011 is the most recent labeling.

On March 16, 2004 (received March 17, 2004) Pharmacia & Upjohn submitted Supplement-035 (S-035) to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The supplement was given an approvable action on January 14, 2005. Pharmacia & Upjohn resubmitted S-035 on September 14, 2005 (received September 16, 2005). The September 14, 2005 submission contained revised labeling for the package insert (PI) and immediate container and carton

labeling as well as proposed labeling for new dosage strength presentations. The DMIHP sent Pharmacia & Upjohn a "Not Approvable" letter for this supplement on March 14, 2006. On September 6, 2006, DMIHP presented the Fragmin review of the CLOT study for the indication extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DT) and/or pulmonary embolism (PE)] to reduce the recurrence of VTE in patients with cancer at the Oncologic Drugs Advisory Committee (ODAC) Advisory Committee meeting held September 6-7, 2006. The Agency was concerned about the disparity of all cause death between the Fragmin arm and the control arm of the study. The Oncologic Drugs Advisory Committee rejected an exploratory analysis by FDA that revealed a mortality safety signal with Pfizer/Eisai's Fragmin in unanimously recommending approval of the low molecular weight heparin for use in cancer patients. On October 10, 2006, DMIHP and Pfizer held a teleconference to discuss the next steps for the efficacy supplement for the use of Fragmin in extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. One of the conclusions was for the sponsor to submit revised labeling.

On February 28, 2007, received March 1, 2007, Pfizer Global Pharmaceuticals (agent for Pharmacia & Upjohn) resubmitted S-035.

Review

In the text below, new sections are indicated in quotation marks. In sections containing revised text, double underlined text indicates proposed additions to the labeling and text with ~~strikeouts~~ indicates proposed deletions.

I. Package Insert

The PI in S-035 (submitted February 28, 2007; received March 1, 2007) identified as "LAB-0058-8.31" Rev December 2006 was compared to the PI in Y-011 (submitted February 28, 2006; received March 1, 2006; accepted March 23, 2007) identified as "818 312 112." The following show the differences between the two PIs.

A. The sponsor deleted all of the colons after the subsection heads **CLINICAL PHARMACOLOGY (Pharmacodynamics, Pharmacokinetics), CLINICAL TRIALS (Prophylaxis of Ischemic complications in Unstable Angina and Non-Q-wave Myocardial Infarction, Prophylaxis of Deep Vein thrombosis in Patients Following Hip Replacement Surgery, Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in patients at Risk for Thromboembolic Complications, Prophylaxis of Deep Vein Thrombosis in Medical Patients at Risk for Thromboembolic Complications Due to Severely Restricted Mobility During Acute Illness), WARNINGS (Hemorrhage, Thrombocytopenia, Miscellaneous), PRECAUTIONS (General, Drug Interactions, Laboratory Tests, Drug/Laboratory Test Interactions, carcinogenicity, Mutagenesis, Impairment of Fertility, Pregnancy,**

Nursing Mothers, Pediatric Use, Geriatric use), ADVERSE REACTIONS (Hemorrhage, Unstable Angina and Non-Q-Wave Myocardial Infarction, Hip Replacement Surgery, Abdominal Surgery, Thrombocytopenia, Other), DOSAGE AND ADMINISTRATION (Unstable Angina and Non-Q-Wave Myocardial Infarction, Hip Replacement Surgery, Abdominal Surgery, Medical Patients with Severely Restricted Mobility During Acute Illness, Administration).

Review Comment: The deletion of the colons throughout the PI is editorial and acceptable.

B. **DESCRIPTION** section

In the first paragraph, third sentence that begins "With reference to the . . ." the sponsor added "12,500, 15,000 or 18,000" after the number "10,000" and added "80, 96 or 115.2" after the number "64" so that the sentence reads "With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each syringe contains either 2500, 5000, 7500, 10,000 12,500, 15,000 or 18,000 anti-factor Xa international units (IU), equivalent to 16, 32, 48, 64, 80, 96 or 115.2[1] mg dalteparin sodium, respectively."

Review Comment: The additions refer to the sponsor's request to add four additional single dose syringe presentations consisting of 10,000 IU/0.4 mL, 12,500 IU/0.5 mL, 15,000 IU/0.6 mL and 18,000 IU/0.72 mL dalteparin sodium for injection (intravenous). The additional numbers are acceptable pending the acceptability of the four new syringe presentations.

C. **CLINICAL PHARMACOLOGY** section

In the first paragraph, third sentence that begins "In man, dalteparin . . . " the sponsor replaced the abbreviation "e.g." with "i.e." so that the sentence reads "In man, dalteparin potentiates preferentially the inhibition of coagulation factor Xa, while only slightly affecting clotting time, i.e., activated partial thromboplastin time (APTT).

Review Comment: APTT is not the only clotting time test that is affected by the inhibition of coagulation factor Xa as prothrombin time is also affected. The revision is not acceptable.

D. **CLINICAL TRIALS** section:

1. Following the **Prophylaxis of Deep Vein Thrombosis in Medical Patients at Risk for Thromboembolic Complications Due to Severely Restricted Mobility During Acute Illness** subsection, the sponsor proposes to add the following new subsection:

"Patients with Cancer and Acute Symptomatic Venous Thromboembolism

(b) (4)

[redacted]

Table (b

(b) (4)

[redacted]

(b) (4)

(b) (4)

(b) (4)

[redacted]

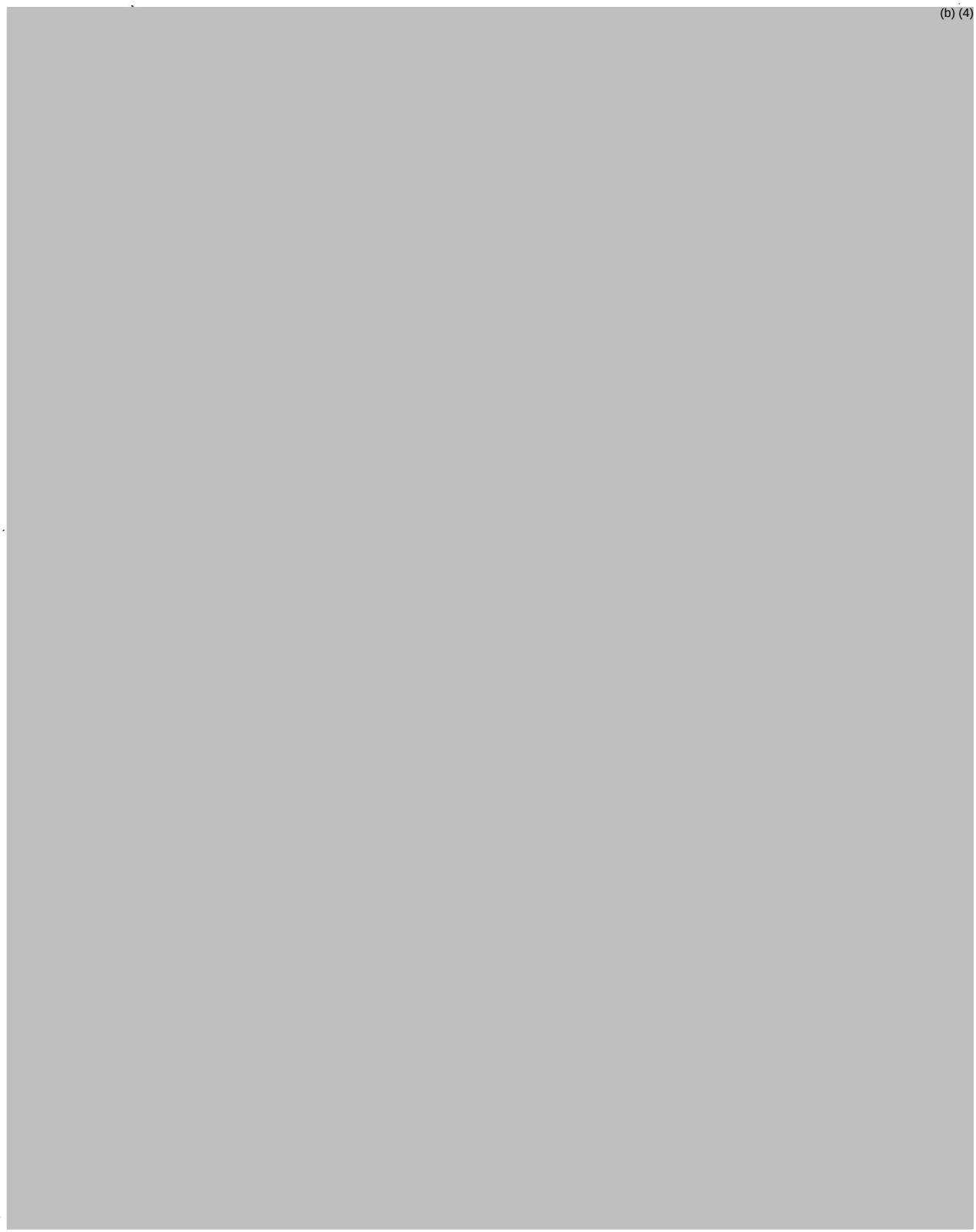
Reviewer Comment:
The sponsor's proposal differs from the Agency's previous proposal as follows. The Agency 's proposed deletions are denoted with strikeouts and the Agency proposed additions are denoted with double underlines.

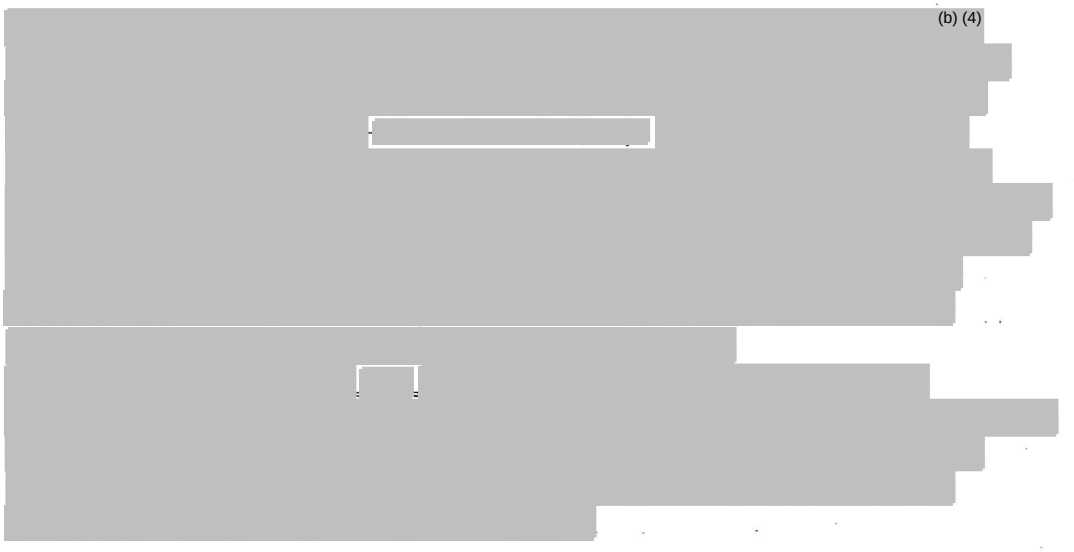
"Patients with Cancer and Acute Symptomatic Venous Thromboembolism:

(b) (4)

[redacted]

(b) (4)





Reviewer Comment: The Medical Officer should comment on this section of the labeling. The discrepancies need to be negotiated with the sponsor.

E. **INDICATIONS AND USAGE section:**

The sponsor proposes to revise the **INDICATIONS AND USAGE** section as follows. The additions are noted with double underlines. Deletions are noted with ~~strikeouts~~.

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

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

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

FRAGMIN is also indicated for the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer."

Reviewer Comment:

The Agency finds the addition of the subsection "CLINICAL TRIALS, Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction" to the first paragraph acceptable.

The Agency prefers the term "6-month treatment" to "extended treatment" in the indication and proposes to delete the phrase "(proximal DVT and/or PE) from the third paragraph so that the third paragraph reads as follows:

FRAGMIN is also indicated for the ~~extended~~ 6-month treatment of symptomatic venous thromboembolism (VTE) (~~proximal DVT and/or PE),~~ to reduce the recurrence of VTE in patients with cancer."

F. **CONTRAINDICATIONS** section

In the second paragraph, first sentence that begins "Patients undergoing regional . . ." the sponsor proposes to add the following phrase "and patients with cancer undergoing regional anesthesia should not receive FRAGMIN for extended treatment of symptomatic VTE" after the word "infarction" and the phrase "for these indications" after the word "recommended" so that the sentence reads "Patients undergoing regional anesthesia should not receive FRAGMIN for unstable angina or non-Q-wave myocardial infarction, and patients with cancer undergoing regional anesthesia should not receive FRAGMIN for extended treatment of symptomatic VTE, due to an increased risk of bleeding associated with the dosage of FRAGMIN recommended for these indications."

Review Comment: The Medical Officer should comment on these proposed revisions.

G. **WARNINGS** section

1. (b) (4) . . .

[redacted]

Review Comment: The proposed addition is not acceptable.

2. **Thrombocytopenia** subsection:

   a. In the first paragraph, the sponsor proposes to add the following sentence as the first sentence of the paragraph "Thrombocytopenia can occur with the administration of FRAGMIN."

   Reviewer Comment:
   The Medical Officer should comment on the acceptability of the proposed new sentence.

   b. In the first paragraph, in the first sentence that begins "In clinical trials, . . . " the sponsor proposes to add "initial FRAGMIN" after the word "In", delete the word [redacted] (b) (4) after the word "trials", add the phrase "in non-cancer populations" after the word "trials", added the phrase "of patients" after the number "<1%" so that the sentence reads as follows;

   "In initial FRAGMIN clinical trials, in non-cancer populations, platelet counts of < 100,000/mm3 and <50,000/mm3 occurred in <1% and <1% of patients, respectively."

   Reviewer Comment: The following is the wording previously proposed by the Agency:

   "In clinical trials supporting the initial approval for FRAGMIN and in subsequent studies in non-cancer populations, thrombocytopenia with platelet counts of < 100,000/mm^3 and < 50,000/mm^3 occurred in < 1% and < 1%, respectively."

   The Medical Officer should comment on the new revision from the sponsor.

   c. In the first paragraph, the sponsor proposes to delete the second sentence that reads [redacted] (b) (4)

   Reviewer Comment:. The proposed deletion is acceptable. This sentence was deleted in the previous FDA proposed revision.

   d. The sponsor proposes to add the following two paragraphs after the revised second sentence:

   [redacted] (b) (4)

(b) (4)

[redacted]

Reviewer Comment: The following two paragraphs were not acceptable in the previous review cycle for this supplement:

(b) (4)

[redacted]

The Medical Officer should comment on the acceptability of the two new paragraphs.

e. In the second paragraph, following the third sentence that reads "The incidence of this complication is unknown at present." The sponsor proposes to add the following sentence; "In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed."

Reviewer Comment: This is the same sentence that was proposed in Cycle 2 of the Coumadin review. The new sentence is acceptable.

f. The FDA proposed to add the paragraph below to this section of the PI.

"In the CLOT study (See CLINICAL TRIALS section), the numerical rate of severe thrombocytopenia (platelet counts less than 50,000/uL) was higher among patients receiving the six-month regimen of Fragmin (19/338, 6%) than among patients receiving Fragmin (approximately five days) followed by OAC to six months (10/335, 3%). Thrombocytopenia, mainly due to chemotherapy, was the

primary reason for modification or interruption of study drug treatment in 27/338, 8% of patients receiving the six-month regimen of Fragmin and 5/335, 2% of patients receiving Fragmin (approximately five days) followed by OAC to six months. Milder degrees of thrombocytopenia (50,000/mcL to < 100,000/mcL) occurred among more subjects receiving Fragmin (approximately five days) followed by OAC to six months (43/335, 43%). In this study two patients in treatment arm A had antibody positive heparin induced thrombocytopenia. In this study there were 57/338, 17% of patients in treatment arm A and 43/335, 43% of patients in treatment arm B that developed platelet counts in the range < 100,000/µl and ≥ 50,000/µl."

Reviewer Comment: The Medical Officer should comment on whether to pursue adding the above paragraph to the PI.

3. **Miscellaneous** subsection

   a. In the first paragraph, in the first sentence that begins "The multiple-dose vial . . ." the sponsor proposes to replace the word "The" with the word "Each" so that the sentence reads "Each 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."

   Reviewer Comment: The word replacement is editorial and acceptable.

   b. In the first paragraph, third sentence that begins "Because benzyl alcohol may . . ." the sponsor proposes to replace the phrase (b) (4) with the phrase "be used with caution" so that the sentence reads "Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should be used with caution in pregnant women (see **PRECAUTIONS, Pregnancy category B, Nonteratogenic Effects**)."

   Reviewer Comment: The Medical Officer should comment on the acceptability of the proposed revision.

H. **PRECAUTIONS section,**

1. **Laboratory Tests** subsection

   a. In the first paragraph, first sentence, the sponsor proposes to add the phrase "blood chemistry" after the phrase "platelet count" so that the sentence reads "Periodic routine complete blood counts, including platelet count, blood chemistry, and stool occult blood tests are recommended during the course of treatment with FRAGMIN."

Reviewer Comment: The Medical Officer should comment on the acceptability of the proposed addition.

b. In the first paragraph, in the second sentence that begins "No special monitoring . . ." the sponsor proposes to add the abbreviation "i.e.," before "APTT" in the parenthetical phrase so that the sentence reads "No special monitoring of blood clotting times (i.e., APTT) is needed."

Reviewer Comment: The addition of the abbreviation is editorial and acceptable.

c. In the second paragraph, in the first sentence that begins "When administered at . . ." the sponsor proposes to add the phrase "the anticoagulant effect of FRAGMIN' after the word "monitoring" so that the sentence reads "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 the anticoagulant effect of FRAGMIN."

Reviewer Comment: The addition of the phrase is editorial and acceptable.

d. Following the second paragraph that begins When administered at . . . " the sponsor proposes to add the following third paragraph:

"Anti-Factor Xa may be used to monitor the anticoagulant effect of FRAGMIN such as in patients with severe renal impairment or if abnormal coagulation parameters or bleeding should occur during FRAGMIN therapy."

Reviewer Comment:
The Medical Officer should comment on the acceptability of the proposed new paragraph.

2. **Drug/Laboratory Test Interactions subsection, *Elevations of Serum Transaminases:* sub-subsection**

a. In the first paragraph, in the first sentence that begins (b) (4)

Reviewer Comment: In the previous review cycle, the proposed sentence without the word (b) (4)

(b) (4) **was found to be acceptable. The Medical Officer should comment on the acceptability of the revised sentence.**

b. Following the first paragraph that begins "In initial FRAGMIN . . ." the sponsor proposes to add the following new paragraph:

(b) (4)

Reviewer Comment: The Medical Officer should comment on the proposed new paragraph.

c. Following the second paragraph that begins "In subsequent FRAGMIN . . ." the sponsor proposes to add the following new paragraph:

"In the FRAGMIN clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated for up to 6 months, asymptomatic increases in transaminase levels, AST and ALT, greater than three times the upper limit of normal of the laboratory reference range have been reported in 8.9% and 9.5% of patients, respectively. The frequencies of Grades 3 and 4 increases in AST and ALT, as classified by the NCI-CTC Scoring System, were 3.0% and 3.8%, respectively. Grades 2, 3 &4 combined have been reported in 12.4% and 13.9% of patients, respectively. (b) (4)

Reviewer Comment:
The Medical Officer should comment on the acceptability of the proposed new paragraph.

3. **Pregnancy: Pregnancy Category B** subsection, **Nursing Mothers** sub-subsection:

The sponsor proposes to delete the first paragraph in the **Nursing Mothers** sub-subsection that reads as follows: (b) (4)

The sponsor proposes to add the following paragraph to the **Nursing Mothers** sub-subsection:

"Limited data are available for excretion of dalteparin in human milk. One study in 15 lactating women receiving prophylactic doses of dalteparin detected small amounts of anti-Xa activity in breast milk, equivalent to a milk/plasma ratio of <0.025-0.224. As

oral absorption of LMWH is extremely low, the clinical implications, if any, of this small amount of anticoagulant activity on the nursing infant are unknown."

Reviewer Comment:

The sponsor proposed this revision in the previous review cycle. The Agency rejected the proposed new paragraph and preferred that the original wording be retained. The proposed paragraph is not acceptable.

4. **Geriatric Use sub-section:**

In the first paragraph, in the first sentence, the sponsor proposes to replace the number (b) (4) with "5516" and the number (b) (4)" with "2237" so that the sentence reads "Of the total number of patients in clinical studies of FRAGMIN, 5516 patients were 65 years of age or older and 2237 were 75 or older."

Reviewer Comment:
The sponsor's proposed revisions are acceptable.

I. **ADVERSE REACTIONS** section

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

The sponsor proposes to revise the table number in the table entitled "**Major Bleeding Events in Unstable Angina and Non-Q-Wave Myocardial Infarction**" from "Table 7" to "Table 8" and revise the reference number from "7" to "8" for the same table in the first sentence of this section so that the sentence reads "Table 8 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction."

Reviewer Comment: The revision is editorial and acceptable pending the acceptability of the new Table 7 (see item I.D.1.).

2. **Hip Replacement Surgery** subsection

The sponsor proposes to revise the table entitled "**Bleeding Events Following Hip replacement Surgery**" from "Table 8" to "Table 9" and revise the reference number from "8" to "9" for the table in the first sentence of this section so that the sentence reads "Table 9 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."

Reviewer Comment: The revision is editorial and acceptable pending the acceptability of the new Table 7 (see item I.D.1.).

3. **Abdominal Surgery** subsection

   The sponsor proposes to revise the table number in the table entitled "**Bleeding Events Following Abdominal Surgery**" from "Table 9" to "Table 10" and revise the reference number from "9" to "10" for the same table in the first sentence of this section so that the sentence reads "Table 10 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients."

   Reviewer Comment: The revision is editorial and acceptable pending the acceptability of the new Table 7 (see item I.D.1.).

4. **Medical Patients with Severely Restricted Mobility During Acute Illness** subsection

   The sponsor proposes to revise the table number in the table entitled "**Bleeding Events in Medical Patients with Severely Restricted Mobility During Acute Illness**" from "Table 10" to "Table 11" and revise the reference number from "10" to "11" for the same table in the first sentence of this section so that the sentence reads "Table 11 summarizes major bleeding events that occurred in a clinical trial of medical patients with severely restricted mobility during acute illness."

   Reviewer Comment: The revision is editorial and acceptable pending the acceptability of the new Table 7 (see item I.D.1.).

5. **Patients with Cancer and Acute Symptomatic Venous Thromboembolism** subsection:

   The sponsor proposes to add the following new section to the PI:

   "Table 12 summarizes the number of patients with bleeding events that occurred in the clinical trial of patients with cancer and acute symptomatic venous thromboembolism. (b) (4)

(b) (4)

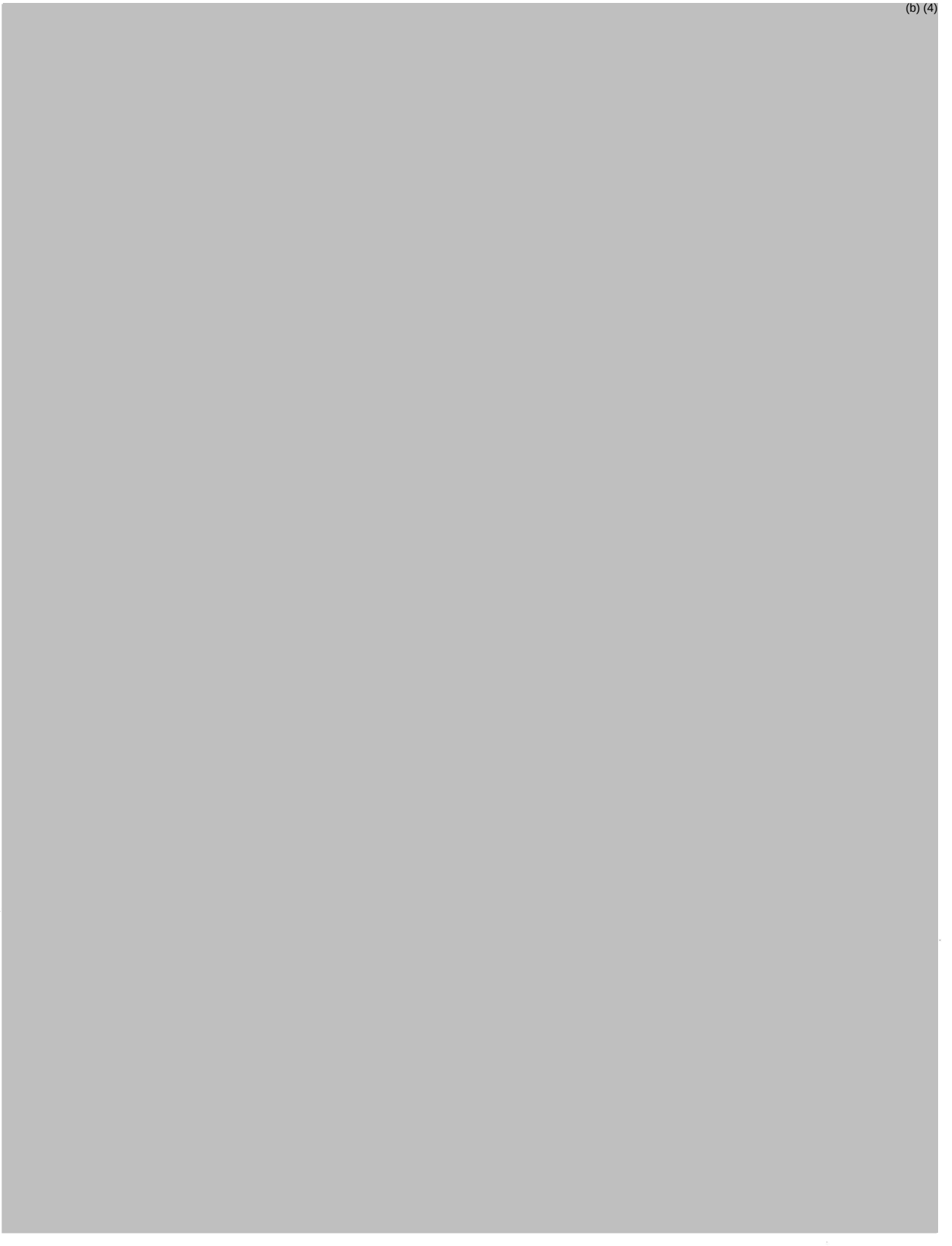
[redacted]

Reviewer Comment: The previous FDA wording was as follows: (double underlines are added words and deleted words are denoted with strikeouts.)

(b) (4)

[redacted]

(b) (4)



[redacted] (b) (4)

The Medical Officer should comment on the acceptability of the proposed new section.

6. ***Ongoing Safety Surveillance*** sub-subsection:

   a. In the first paragraph, in the first sentence that begins "Since first international . . ." the sponsor proposes to replace the word [redacted] (b) (4) with the phrase "more than 15" so that the sentence reads: "Since first international market introduction in 1985, there have been more that 15 reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture."

   Reviewer Comment:
   The Medical Officer should comment no the proposed revision.

   b. In the first paragraph, in the second sentence that begins "Five of the nine patients . . ." the sponsor proposes to replace the phrase [redacted] (b) (4) with "The majority of" so that the sentence reads: "The majority of patients had post-operative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis."

   Reviewer Comment:
   The Medical Officer should comment no the proposed revision.

c. In the first paragraph, the sponsor proposes to delete the third and fourth sentences that read: (b) (4)

Reviewer Comment:
The sponsor's proposed deletions are acceptable.

d. In the first paragraph following the fourth sentence that begins " (b) (4) the sponsor proposes to add the following sentence: "In some cases the hematoma resulted in long-term or permanent paralysis (partial or complete)."

Reviewer Comment:
The sponsor's proposed addition is acceptable.

7. (b) (4)

There have been isolated cases of alopecia reported that improved on drug discontinuation."

Reviewer Comment:
The proposed addition is not acceptable.

J. **DOSAGE AND ADMINISTRATION** section

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

The sponsor proposes to revise the table number in the table entitled "Table 11 Volume of FRAGMIN to be Administered by Patient Weight, Based on 9.5 mL Vial (10,000 IU/mL)" from "Table 11" to "Table 13" and revise the reference number from "11" to "13" for the same table in the second paragraph, first sentence of this section so that the sentence reads "Table 13 lists the volume of FRAGMIN, based on the 9.5 mL multiple-dose vial (10,000 IU/mL), to be administered for a range of patient weights."

Reviewer Comment: The revision is editorial and acceptable pending the acceptability of the new Table 7 (see item I.D.1. and I.I.5.).

2. (b) (4) subsection

The sponsor proposes to revise the table number in the table entitled "Table 12 Dosing Options for Patients Undergoing Hip Replacement Surgery" from "Table 12" to "Table 14" and revise the reference number from "12" to "14" for the same table in the first paragraph, first sentence of this section so that the sentence reads "Table 14 presents the dosing options for patients undergoing hip replacement surgery."

Reviewer Comment: The revision is editorial and acceptable pending the acceptability of the new Table 7 (see item I.D.1. and Item I.I.5.).

K. **Treatment** (b) (4) **Venous thromboembolism in Patients with Cancer** subsection

Following the subsection entitled **Medical Patients with Severely Restricted Mobility During Acute Illness,** the sponsor proposes to add the following text and tables.

"**Treatment** (b) (4) **Venous Thromboembolism in Patients with Cancer:**

In patients with cancer and venous thromboembolism, the recommended dosing of FRAGMIN is as follows: for the first 30 days of treatment administer FRAGMIN 200 IU/kg total body weight subcutaneously (s.c.) once daily. The total daily dose should not exceed 18,000 IU. Table 15 lists the dose of FRAGMIN to be administered once daily during the first month for a range of patient weights.

Month 1:

Table 15
Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during the First Month

Body Weight (lbs)	Body Weight (kg)	FRAGMIN Dose (IU) (pre-filled syringe) qd s.c.
< 123.2	< 56	10,000
125.4 to 149.6	57 to 68	12,500
151.8 to 180.4	69 to 82	15,000
182.6 to 215.6	83 to 98	18,000
≥ 217.8	≥ 99	18,000

Months 2 to 6:

Administer FRAGMIN at a dose of approximately 150 IU/kg, s.c. once daily during Months 2 through 6. The total daily dose should not exceed 18,000 IU. Table 16 lists the volume of FRAGMIN to be administered once daily for a range of patient weights during months 2-6.

Table 16
Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during Months 2-6

Body Weight (lbs)	Body Weight (kg)	FRAGMIN Dose (IU) (pre-filled syringe) qd s.c.
< 124	≤ 56	7,500
125 to 150	57 to 68	10,000
151 to 181	69 to 82	12,500
182 to 216	83 to 98	15,000
≥ 217	≥ 99	18,000

Safety and efficacy beyond six months has not been evaluated in patients with cancer and acute symptomatic venous thromboembolism (see **WARNINGS, Thrombocytopenia** and **ADVERSE REACTIONS. Patients with Cancer and Acute Symptomatic Venous Thromboembolism**).

Dose reductions for thrombocytopenia in patients with cancer and acute symptomatic venous thromboembolism

(b) (4)

Dose reductions for renal insufficiency in patients with cancer and acute symptomatic venous thromboembolism

(b) (4)

Reviewer Comment: In the previous review cycle, DMIHP recommended the following wording to this section: (Note: The additions are noted with double underlines. Deletions are noted with ~~strikeouts~~.)

(b) (4)

[redacted]

(b) (4)



The Medical Officer should comment on the revised proposed section.

L. **HOW SUPPLIED section**

Following the first sentence that reads "FRAGMIN Injection is available in the following strengths and package sizes:" the sponsor proposes to replace the current **HOW SUPPLIED** section that reads:

"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.

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

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].

Rx only

U.S. Patent 4,303,651

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

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

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

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

818 312112 Revised March 2004"

To read:

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

(b) (4)

[redacted]

(b) (4)



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

Rx only

Manufactured for

Eisai Inc.

Teaneck, NJ 07666

Manufactured by

Pfizer Inc

New York, NY 10017
Made in Belgium
(multiple-dose vials)

Jointly manufactured by

Pfizer Inc, New York, NY 10017
and Vetter Pharma-Fertigung, GmbH & Co. KG
Ravensburg, Germany
(prefilled syringes)

LAB-0058-8.1
Revised December 2006"

Reviewer Comment:

The sponsor of this NDA (Pharmacia & Upjohn Company) is a subsidiary of Pfizer, Inc. Pfizer is part of the Eisai Inc. family. The sponsor's proposed revisions to the HOW SUPPLIED section update the manufacturer NDC numbers and manufacturing information. The proposed revisions to this section are editorial and acceptable.

II. Immediate container labeling

The sponsor proposes to add four new presentations of Fragmin to administer Fragmin for the new indication for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The immediate container labeling format for the new dosage strengths are the same as the previously approved strengths (2500 IU/0.2 mL; 5000 IU/0.2 mL; 7500 IU/0.3 mL and 10,000 IU/1.0 mL) except for the following:

A. The sponsor added a box around the tradename "Fragmin® dalteparin sodium injection" for each new dosage strength in the same color as in the box below with the dosage strength for that presentation.

Reviewer Comment: The revision is editorial and acceptable.

B. The sponsor revised the manufacturing information from "Manufactured for Pharmacia & Upjohn Company" to "Manufactured for Eisai Inc. Teanneck NJ 07666."

Reviewer Comment: The revision is editorial and acceptable.

C. The sponsor added new identification codes for each new dosage strength as follows:

10,000 IU/0.4 mL	ID: 200480 5Q8796 KV1017-01
12,500 IU/0.5 mL	ID: 200481 5Q8797 KV1021-01
15,000 IU/0.6 mL	ID: 200482 5Q8799 KV1025-01
18,000 IU/0.72 mL	ID: 200483 5Q8801 KV1029-01

Reviewer Comment: The revisions are editorial and acceptable.

D. The colors given to the new dosage strengths are as follows:

(b) (4)

Reviewer Comment: The following colors are similar to the existing colors for the already approved presentations:
2500 IU/0.2 mL, (sky blue) and the 18,000 IU/0.72 mL (b) (4)
5000 IU/0.2 mL (orange) and the 12,500 IU/0.5 mL (b) (4)
7500 IU/0.3 mL (light green) and the 10,000 IU/0.4 mL (b) (4)

In addition, the proposed 10,000 IU per 0.4 mL is similar to the already approved 10,000 IU per 1.0 mL strength. There is concern that the above syringes could easily be mixed up, causing the wrong dose to be administered. The proposed color schemes for the new presentations are unacceptable. The new colors should be discussed with the Division of Medical Errors and Technical Services (DMETS).

III. Blister labeling

The sponsor proposes to add four new presentations of Fragmin to administer Fragmin for the new indication for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The blister covering labeling format for the new dosage strengths are the same as the previously approved strengths (2500 IU/0.2 mL; 5000 IU/0.2 mL; 7500 IU/0.3 mL and 10,000 IU/1.0 mL) except for the following:

A. The sponsor deleted the leaf from the tradename Fragmin®.

Review Comment: The revision is editorial and acceptable.

B. The sponsor revised the labeling from one column to two columns. The sponsor also moved the storage conditions that read "Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]" from the third line to the first line in the first column.

Review Comment: The revision is editorial and acceptable.

C. The sponsor revised the phrase "See package insert" to read "See accompanying prescribing information" and moved it from the third line (below the tradename) to the left column below the storage conditions.

Review Comment: The revision is editorial and acceptable.

D. The sponsor revised the manufacturing information from "Manufactured for Pharmacia & Upjohn Company" to "Manufactured for Eisai Inc. Teanneck NJ 07666" and moved it

from the fourth line to the left column below the sentence that reads "See accompanying prescribing information" (the bottom of the left hand column).

Reviewer Comment: The revision is editorial and acceptable.

E. The sponsor added new identification codes for each new dosage strength as follows:

10,000 IU/0.4 mL	ID: 200484 KV101B-01 5T1171
12,500 IU/0.5 mL	ID: 200485 KV1022-01 5T1172
15,000 IU/0.6 mL	ID: 200486 KV1026-01 5T1174
18,000 IU/0.72 mL	ID: 200487 KV1029-01 5T1176

Reviewer Comment: The revision is editorial and acceptable.

F. The colors given to the new dosage strengths are as follows:
(b) (4)

Reviewer Comment: The following colors are similar to the existing colors for the already approved presentations:
2500 IU/0.2 mL, (sky blue) and the 18,000 IU/0.72 mL (b) (4)
5000 IU/0.2 mL (orange) and the 12,500 IU/0.5 mL (b) (4)
7500 IU/0.3 mL (light green) and the 10,000 IU/0.4 mL (b) (4)

In addition, the proposed 10,000 IU per 0.4 mL is similar to the already approved 10,000 IU per 1.0 mL strength. There is concern that the above syringes could easily be mixed up, causing the wrong dose to be administered. In addition, the colors are pale and the writing is difficult to read on the proposed blister labeling. The proposed color schemes for the new presentations are unacceptable. The new colors should be discussed with the Division of Medical Errors and Technical Services (DMETS).

IV. Carton Labeling

The sponsor proposes to add four new presentations of Fragmin to administer Fragmin for the new indication for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The carton container labeling format for the new dosage strengths are the same as the previously approved strengths (2500 IU/0.2 mL; 5000 IU/0.2 mL; 7500 IU/0.3 mL and 10,000 IU/1.0 mL) except for the following:

A. Back Panel

The sponsor moved the storage information from the back panel to horizontally on the left side panel. The sponsor also revised the text from the following:

"Usual dosing: See package insert for complete product information
Store at controlled room temperature 20 to 25C (68 to 77F) [see USP]
Each XX mL contains:
Dalteparin Sodium XXX IU (anti-Xa) Equivalent to YY mg)
Water for injection to ZZZ 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"

To:

Store at controlled room temperature 20 to 25 C (68-77F) [see USP]
Dosage and Use: See accompanying prescribing information
Each XXX IU (anti-Xa) (equivalent to YY mg)
and water for injection to ZZZ mL sodium chloride is added to achieve isotonicity.

Fragmin is a registered trademark of Pfizer Health AB and is licensed to Eisai Inc © 2006 Eisai, Inc."

Reviewer Comment: The information is essentially the same except for the new manufacturing company. The change of location and text are editorial and acceptable.

B. Front Panel

The sponsor added the same information on the front panel to the back panel. The revisions to the current front panel are as follows:

1. The sponsor moved the Rx only symbol from the bottom left of the front panel to the top right of the front panel below the NDC number.

   Reviewer Comment: The revision is editorial and acceptable.

2. The sponsor deleted the leaf from the tradename Fragmin®.

   Reviewer Comment: The revision is editorial and acceptable.

3. The sponsor removed the two solid lines before and after the tradename and added an unfilled box around the tradename in the color designated for the particular dosage strength.

   Reviewer Comment: The revision is editorial and acceptable.

4. The sponsor moved the phrase "for subcutaneous injection" from after the dosage strength to after the tradename and before the dosage strength on panel.

   Review Comment: The revision is editorial and acceptable.

5. The sponsor revised the manufacturing information from "Pharmacia" to "(Eisai logo) Manufactured for Eisai Inc. Teanneck NJ 07666 (Pfizer logo) Jointly manufactured by Pfizer, Inc. New York, NY 10017 and Vetter Pharma-Fertigung GmbH and Co. KG Ravensburg, Germany" and moved it from the bottom right of the panel to the bottom left of the panel.

   Reviewer Comment: The revision is editorial and acceptable.

6. The sponsor added new identification codes for each new dosage strength as follows:

   10,000 IU/0.4 mL
   NDC 62856-100-10 ID: 8P7750 KV1015-01

   12,500 IU/0.5 mL
   NDC 62856-125-10 ID: 8P7752 KV1019-01

   15,000 IU/0.6 mL
   NDC 62856-150-10 ID: 8P7755 KV1023-01

   18,000 IU/0.72 mL
   NDC 62856-180-10 ID: 8P7758 KV1027-01

   Reviewer Comment: The revision is editorial and acceptable.

7. The colors given to the new dosage strengths are as follows

   (b) (4)

   Reviewer Comment: The following colors are similar to the existing colors for the already approved presentations:

2500 IU/0.2 mL, (sky blue) and the 18,000 IU/0.72 mL (b) (4)
5000 IU/0.2 mL (orange) and the 12,500 IU/0.5 mL (b) (4)
7500 IU/0.3 mL (light green) and the 10,000 IU/0.4 mL (b) (4)

There is concern that the above syringes could easily be mixed up, causing the wrong dose to be administered. The proposed color schemes for the new presentations are unacceptable. The new colors should be discussed with the Division of Medical Errors and Technical Services (DMETS).

C. Top Flap (lid)

The sponsor deleted the NDC number from the top flap (lid). The sponsor also deleted the dosage strength. The sponsor added the phrase "For subcutaneous injection."

The addition of "For subcutaneous injection" and the deletion of the NDC number are editorial and acceptable. The dosage strength should be retained on the top flap so the proper strength can be ascertained more easily.

Conclusions

1. The following items are editorial and acceptable: I.A., I.G.3.a., I.H.1.b., I.H.c., I.L., II.A., II.B., II.C., III.A., III.B., III.C., III.D., III.E., IV.A. and I.V.B.1-6.

2. The following items are acceptable: I..2.c., I.G.2.e., I.H.4., I.I.6.c. and I.I.6.d.

3. The following items are not acceptable: I.C., I.G.1., I.H.3., II.7., II.D., III.F., IV.B.7., and IV.C.

4. The following items need to be reviewed by the Medical Officer: I.D.1., I.F., I.G.2.a., I.G.2.b., I.G.2.d., I.G.2.f., I.G.3.b., I.H.1.a., I.H.1.d., I.H.2.a., I.H.2.b., I.h.2.c., I.I.5., I.I.6.a.

5. The following items are acceptable pending the acceptance of the proposed new syringe presentations: I.I.1., I.I.2., I.I.3., I.I.4.

6. The following are acceptable pending the acceptance of Table 7: I.J.1., I.J.2.,

7. Item I.E. should be revised according to the FDA recommendations.

8. The Office of Drug Safety, Division of Medical Errors and Technical Support should be consulted for comment on the proposed revised immediate container, blister labeling and carton labeling.

9. It is this reviewer's opinion that the sponsor should propose revised color schemes for the new presentations that are sufficiently different from the already approved presentations to

ensure that the presentations are not confused with each other. The proposed immediate container, blister labeling and carton labeling should not be approved. The PI may or may not be approved pending review by the medical officer and labeling negotiations with the sponsor.

Diane Leaman, B.S.
Regulatory Health Project Manager
Division of Medical Imaging and
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Drafted: dl/March 30, 2007
Initialed: A.Kacuba 4.4.07
Finalized: April 6, 2007
Filename: N20287S035RPMLblrevCycle3.doc

RPM LABELING REVIEW

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

/s/

Diane V Leaman
4/5/2007 03:56:22 PM
CSO

Alice Kacuba
4/5/2007 06:52:39 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Drug Safety/Division of Medical Errors and Technical Support
Mail: ODS

FROM: Diane Leaman

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 2, 2007		20-286/S-035	Efficacy Supplement/Labeling	February 28, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fragmin (dalteparin sodium, injection)	Rush	Low molecular weight heparin	April 16, 2007

NAME OF FIRM: Pfizer Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
This is the sponsor's response to the March 14, 2006 not approvable letter for the efficacy supplement S-035 for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to reduce the recurrence of VTE in patients with cancer. The package insert (PI) is attached. The sponsor is also proposing four new dosage strengths and syringe presentations (immediate container, blister labeling and carton labeling). The package format for the labeling has been revised.
Please review the new presentations of 10,000 IU, 12,500 IU, 18,000 IU in comparison to the already approved product labeling for Fragmin 2500 IU, 5,000 IU, 7500 IU, 10,000 IU, preassembled syringes and the 10,000 IU and 25,000 IU multiple-dose vials.

This is an electronic submission. The labeling can be found at http://cdernet.fda.gov/edr/ under NDA 20-287/S-035 dated February 28, 2007 (SE1) AZ. This is a two month review cycle.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

38 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Diane V Leaman
4/2/2007 06:29:01 PM

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

OFFICE OF DRUG SAFETY

(White Oak Mail Stop 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 05-0143-1
February 21, 2006	February 28, 2006	
DOCUMENT DATES:		
September 14, 2005 and		
February 17, 2006		

TO: George Q. Mills, M.D.
Director, Division of Medical Imaging and Hematology Products

THROUGH: Jinhee Jahng, Pharm.D., Acting Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Laura L. Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Fragmin**
(dalteparin sodium injection)
10,000 IU (anti-factor Xa)/0.4 mL
12,500 IU (anti-factor Xa)/0.5 mL
15,000 IU (anti-factor Xa)/0.6 mL
18,000 IU (anti-factor Xa)/ 0.72 mL

NDA #: 20-287/S-035

NDA SPONSOR: Pfizer Global Pharmaceuticals

RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; White Oak Mail Stop 4447
Center for Drug Evaluation and Research

LABELING REVIEW

DATE OF REVIEW: **March 3, 2006**

NDA# 20-287/S-035

NAME OF DRUG: **Fragmin**
(dalteparin sodium injection)
10,000 IU (anti-factor Xa)/0.4 mL
12,500 IU (anti-factor Xa)/0.5 mL
15,000 IU (anti-factor Xa)/0.6 mL
18,000 IU (anti-factor Xa)/ 0.72 mL

NDA HOLDER: Pfizer Global Pharmaceuticals

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Medical Imaging and Hematology Products for assessment of the container labels, carton, and insert labeling for Fragmin. Specifically, the Division has requested that DMETS review the four new syringe strengths [10,000 IU (anti-factor Xa)/0.4 mL, 12,500 IU (anti-factor Xa)/0.5 mL, 15,000 IU (anti-factor Xa)/0.6 mL, and 18,000 IU (anti-factor Xa)/ 0.72 mL] in support of the efficacy supplement (S-035) for the additional indication of extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer.

PRODUCT INFORMATION

FRAGMIN Injection (dalteparin sodium injection) is a low molecular weight heparin (LMWH). 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, 10,000, 12,500, 15,000 or 18,000 anti-Factor Xa international units (IU), equivalent to 16, 32, 48, 64, 80, 96 or 115.2 mg dalteparin sodium, respectively. Each multiple dose 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.

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

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

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

The proposed efficacy supplement adds a new indication for the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer. The dosing recommendations for the new indication are as follows:

Treatment and Reduction of Venous Thromboembolism in Patients with Cancer:

In patients with venous thromboembolism and cancer, the recommended dosing of FRAGMIN is as follows: for the first 30 days of treatment administer FRAGMIN 200 IU/kg total body weight subcutaneously (s.c.) once daily. The total daily dose should not exceed 18,000 IU. The table lists the dose of FRAGMIN to be administered once daily during the first month for a range of patient weights.

Month 1: Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during the First Month

Body Weight (lbs)	**Body Weight (kg)**	**FRAGMIN Dose (IU) (pre-filled syringe)** Daily
(b) (4)	< 56	10,000
	57 to 68	12,500
	69 to 82	15,000
	83 to 98	18,000
	≥ 99	18,000

Months 2 to 6: Administer FRAGMIN at a dose of approximately 150 IU/kg, subcutaneously. once daily during Months 2 through 6. The total daily dose should not exceed 18,000 IU. The table on page 4 lists the volume of FRAGMIN to be administered once daily for a range of patient weights during months 2-6.

Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during Months 2-6

Body Weight (lbs)	**Body Weight (kg)**	**FRAGMIN Dose (IU) (pre-filled syringe) daily**
(b) (4)	≤ 56	7,500
	57 to 68	10,000
	69 to 82	12,500
	83 to 98	15,000
	≥ 99	18,000

Due to the dosage recommendations for the new indication, four new syringe strengths are proposed which contain the Fragmin 25,000 IU (anti-factor Xa)/1 mL concentration:

10,000 IU (anti-factor Xa)/0.4 mL
12,500 IU (anti-factor Xa)/0.5 mL
15,000 IU (anti-factor Xa)/0.6 mL
18,000 IU (anti-factor Xa)/ 0.72 mL

Refer to Appendix A for the complete list of proposed Fragmin strengths and package sizes.

II. RISK ASSESSMENT:

ADVERSE EVENT REPORTING SYSTEM (AERS) and DRUG QUALITY REPORTING SYSTEM (DQRS)

DMETS conducted a search of the Adverse Event Reporting System (AERS) to determine if any postmarketing safety reports of medication errors associated with Fragmin were reported since approval. The preferred terms "Pharmaceutical Product Complaint," "Treatment Noncompliance," "Medication Error," Accidental Exposure," "Underdose," "Intercepted Medication Error," "Circumstance or Information Capable of Leading to Medication Error," "Drug Prescribing Error," and "Drug Dispensing Error" were used. AERS searches were run for "Fragmin" and "Dalteparin Sodium". The Drug Quality and Reporting System (DQRS) database was searched for similar medication error reports. A total of eight (n=8) pertinent medication errors were retrieved in the AERS and DQRS searches. Since seven of the medication errors pertained to Fragmin multi-dose vials, and are not relevant to this consult, they will be discussed in a forthcoming DMETS post-marketing consult (ODS Consult # 05-0413). The eighth case, which involved the warnings in the package insert will be discussed in this review and in the post-marketing consult.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels, carton and insert labeling of Fragmin, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential error.

A. GENERAL COMMENTS

1. DMETS notes that the colors for the proposed syringe strengths are similar to colors already used for existing syringe strengths. There is concern that the strengths with similar colors could easily be confused, leading to selection errors and resulting in the wrong dose to be administered. We recommend that each syringe have a different, distinguishable color which may help practitioners differentiate between the Fragmin strengths, and thus reduce the potential for selection errors.

a. [redacted] (b) (4)

b. [redacted] (b) (4) presentations

DMETS notes that the 2500 IU/0.2 mL vial features the current Pharmacia and Upjohn configuration which differs in presentation from the labels submitted by Pfizer. When all the labels and labeling are changed to be consistent with the change in ownership to Pfizer, the labels will look even more similar.

[redacted] (b) (4)

c. [redacted] (b) (4) color presentations

DMETS notes that the 5000 IU/0.2 mL vial features the current Pharmacia and Upjohn configuration which differs in presentation from the labels submitted by Pfizer. When all the labels and labeling are changed to be consistent with the change in ownership to Pfizer, the labels will look even more similar.

[redacted] (b) (4)

2. CONTAINER LABELS (Blister Backing for Syringes)

The size and color of the font on the syringe blister backing is difficult to read. In particular, the [redacted] (b) (4) colors are the most difficult to read. Revise the colors to improve readability or increase the font size and prominence accordingly. The Sponsor may also wish to consider using black font for the text and using color blocking for the strength, similar to the presentation of the syringe strength on the container labels and carton labeling.

[redacted] (b) (4)

B. INSERT LABELING

1. We note a typographical error in Table 1 on page 3 of the insert labeling. Specifically, the Fragmin Dosing Regimen heading should read 120 IU/kg **q** 12hr s.c. (emphasis added). The "q" was omitted in the draft insert labeling. However, we recommend avoiding the use of all abbreviations in the labels and labeling since they are often misread and may lead to medication errors (i.e., "q", "s.c.", "qd", "bid", etc.). As evidenced by our post-marketing surveillance, abbreviations and acronyms may be misinterpreted. We note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2006 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must 'Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization'. The abbreviation "q.d." is specifically listed as a dangerous abbreviation, acronym or symbol. Additionally, the Institute for Safe Medication Practices also publishes an "ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations" in which they also recommend avoiding the use of the abbreviation "q.d." Postmarketing experience has shown that "q.d." (once daily) may be confused with "q.i.d." (four times daily), especially if the period after the letter "q" or the tail of the letter "q" is misinterpreted as the letter "i". Revise accordingly (i.e., "q" to ready "every", "qd" to read "daily", "bid" to read "twice daily", "s.c." to read "subcutaneously", etc.).

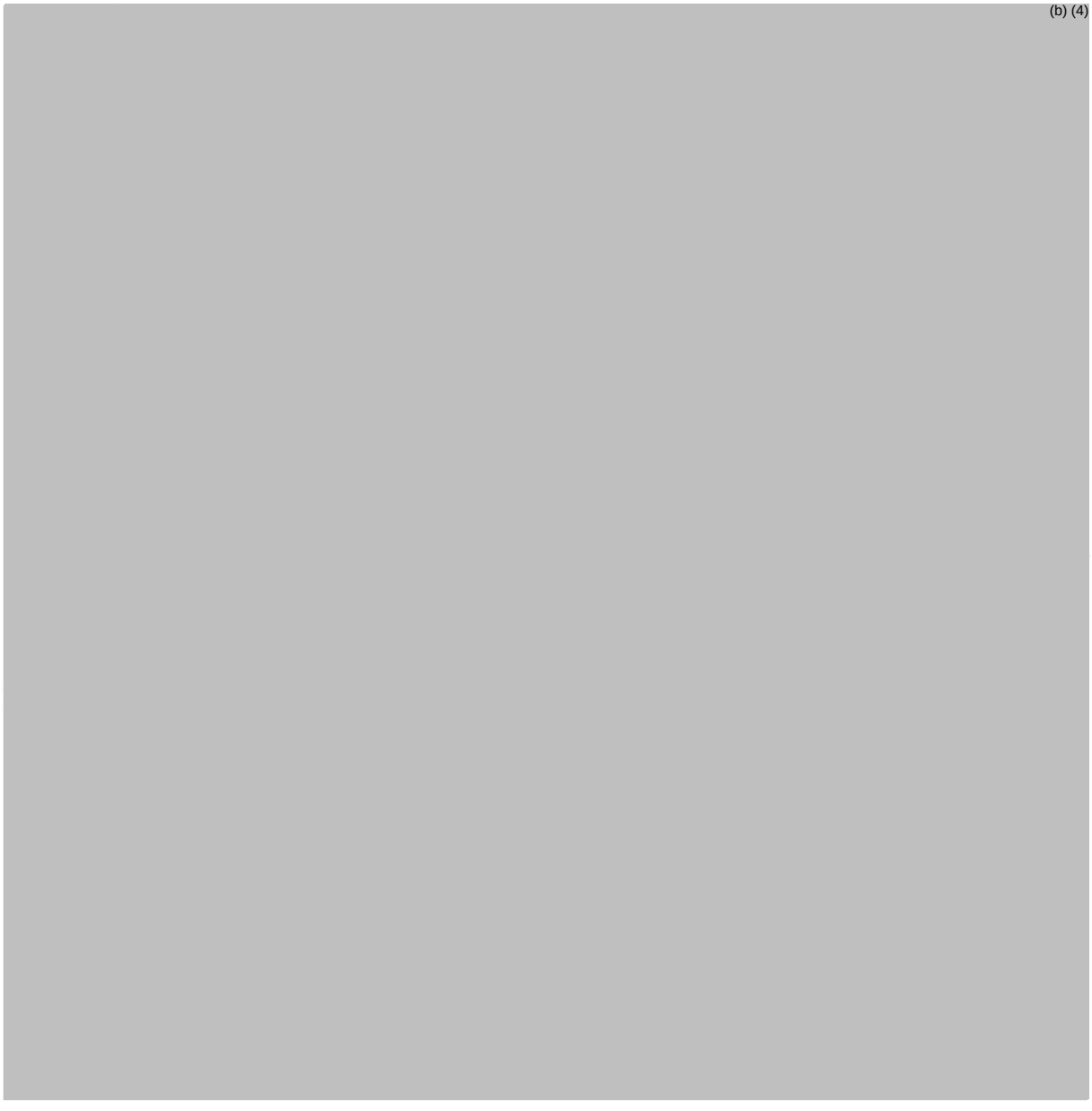
2. We note the use of a terminal zero on page 24 of the package insert labeling in the HOW SUPPLIED chart. We recommend that you avoid the use of terminal zeroes for expressions of numbers in all labels and labeling (i.e., 1 mL and not 1.0 mL) since it may result in misinterpretation of the number if the decimal point is not noticed. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs....the quantity of active ingredient when expressed in whole numbers shall be shown WITHOUT a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as the Institute for Safe Medication Practices list terminal zeroes on their dangerous abbreviations and dose designations list.

3. We recommend you change the heading of the MISCELLANEOUS sub-section in the WARNINGS section, to more accurately reflect the recommendation that the Fragmin multi-dose vials, preserved with benzyl alcohol (b) (4) The MISCELLANEOUS heading is non-specific as to the content of the section, and is easy for the reader to overlook. However, we also note that in a proposed version of the insert labeling (S-035), the warning has been changed from the wording that Fragmin (b) (4) to "should be used with caution in pregnant women." The section now reads:

Each 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 be used with caution in pregnant women (see PRECAUTIONS, Pregnancy Category B, Nonteratogenic Effects).

DMETS cannot comment on the clinical significance of using the Fragmin multi-dose vial with benzyl alcohol in pregnant women, but regardless of the strength of the warning used, the heading should more accurately reflect the contents of the warning in the section.

Appendix A: FRAGMIN Injection is proposed to be available in the following strengths and package sizes (new syringe strengths are highlighted):



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/s/

Laura Pincock
3/14/2006 03:35:19 PM
DRUG SAFETY OFFICE REVIEWER

Jinhee Jahng
3/14/2006 03:39:41 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/14/2006 04:43:28 PM
DRUG SAFETY OFFICE REVIEWER

Tertiary Review Memorandum to the File

NDA:	020-287, supplement 35
Product:	Dalteparin for use among cancer patients
Sponsor:	Pharmacia
Submission date:	September 14, 2005
Today's date:	March 13, 2006
Reviewer:	Dwaine Rieves, MD; Deputy Division Director, DMIHP

1. Overview and Reviewer Conclusions:

This supplement was originally submitted on March 16, 2004. In the submission, the sponsor supplied a single clinical study (the "CLOT") study to support a new indication for the use of fragmin in the treatment of cancer patients with venous thromboembolism (VTE). FDA provided an approvable letter to the sponsor on January 14, 2005. In the approvable letter, FDA cited certain safety concerns that necessitated additional CLOT analyses as well as a need for the sponsor's commitment to certain post-marketing studies. The major safety concerns cited in the approvable letter related to the need for additional analyses of liver test abnormalities.

The sponsor responded to the January 14, 2005 approvable letter by submiting the requisite information on September 14, 2005. FDA performed a review of the newly submitted material in the context of the original review of the CLOT study.

FDA has determined that the submitted data do not provide substantial evidence of the safety and efficacy of dalteparin for the proposed indication. Within the action letter, the sponsor will receive specific directions regarding the recommended course of action, including the opportunity for a meeting with FDA to plan a response to the action letter. I concur with the FDA findings and action plan.

2. The major FDA findings:

1. The submitted clinical data do not provide sufficient evidence of the safety of dalteparin for the proposed indication. Specifically, the supplied data no not rule out a clinically important association of dalteparin with a mortality disadvantage when compared to oral anticoagulation. The basis for this concern is summarized below.

2. The major source of clinical data supporting the safety and efficacy of dalteparin for the proposed indication is derived from the clinical study entitled, "Randomized comparison of low molecular weight heparin (Dalteparin, Fragmin) versus oral anticoagulant therapy for long term anticoagulation in cancer patients with venous thromboembolism." This study is referred to as the "CLOT" study. In this study, 677 patients were randomized to either the study agent group (dalteparin) or the control group (oral anticoagulant, OAC). The study agent regimens, administered in an open label manner, were supposed to extend over a six month period for both study groups.

a. Compliance with the proposed treatment duration was very limited for both study groups. Specifically, approximately 50% of the randomized patients completed the assigned study drug regimens. Patients and investigators discontinued the assigned drug regimens for a variety of reasons, including certain subjectively determined reasons as well as the occurrence of death and adverse events.

b. The study's primary endpoint result, time to first recurrence of a symptomatic venous thromboembolic event (VTE), was the finding of a statistically significant treatment effect for patients in the dalteparin group.

c. The major safety finding related to an excess in study drug discontinuations due to death in the dalteparin group (17.5%) compared to the OAC group (6.3%). Other safety observations related to numerically higher rates of major bleeding and thrombocytopenia among patients in the dalteparin group.

d. The excess of patients in the dalteparin group who discontinued the assigned study drug regimen due to death provides evidence that dalteparin may have contributed to an excess in "on treatment" mortality even though the overall cumulative mortality rates were similar between the two study groups. Analyses that attempt to adjust for the "time on treatment" do not resolve the imbalance in the rates of study drug regimen discontinuation due to death. These data, although derived from a single clinical study that used an open label design, provide evidence that dalteparin may have contributed to an excess of deaths in the cancer patient population.

e. The rates of the "on treatment" deaths are similar to those for the rates of the first VTE recurrence and raise the possibility that the study's primary endpoint result may have been confounded by the imbalance in "on treatment" deaths.

These findings were briefly reviewed with the sponsor in a telephone conversation in early March, 2006. In this telephone conversation, the sponsor was invited to request a meeting with FDA to discuss the response to FDA review findings. FDA also expressed concern regarding the limited public disclosure of the safety findings from the CLOT study. FDA stated that these issues would be addressed in the FDA letter response to the sNDA submission.

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/s/

Rafel Rieves
3/13/2006 02:50:59 PM
MEDICAL OFFICER

REGULATORY PROJECT MANAGEMENT LABELING
Division of Medical Imaging and Hematology Products (DMIHP)

Application Number: NDA 20-287/S-035

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

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

Materials Reviewed: Package Insert (PI)
- Immediate container labels
- Blister labeling
- Carton labeling

Submission Date: September 14, 2005
Receipt Date: September 15, 2005

Background and Summary

Fragmin is a low molecular weight heparin (LMWH) product. The 2500 IU strength was approved December 22, 1994, for use in the prophylaxis of deep venous thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery, who are at risk of thromboembolic complications. The 5,000 IU dosage form was approved March 18, 1996, for prevention of DVT in patients at high risk. Fragmin was approved for prophylaxis of DVT which may lead to PE in patients undergoing hip replacement surgery on March 30, 1999. Fragmin was approved for treatment of unstable angina and non-Q-wave myocardial infarction for the prevention of ischemic complications in patients on concurrent aspirin therapy on May 25, 1999. The 10,000 IU syringe was approved November 14, 2000.

Pfizer Global Pharmaceuticals (Pfizer) merged with Pharmacia and Upjohn on April 14, 2003. Pharmacia and Upjohn remains the sponsor of NDA 20-287. Pfizer is the authorized agent for Pharmacia and Upjohn for this NDA.

Pfizer submitted Supplement-034 as a Changes Being Effected (CBE) labeling supplement (submitted September 8, 2003; received September 9, 2003) to revise the instructions in the FRAGMIN package insert (PI) that instruct the user to expel the air bubble prior to using the FRAGMIN graduated syringe. Supplement S-034 was amended with revised FPL on March 26, 2004 (received March 29, 2004) and was approved April 21, 2004.

Pfizer submitted annual report Y-010 on February 28, 2005 (received March 1, 2005). The labeling in Y-010 is the most recent labeling.

On March 16, 2004 (received March 17, 2004) Pharmacia & Upjohn submitted Supplement-035 (S-035) to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The supplement was given an approvable action on January 14, 2005. Pharmacia & Upjohn resubmitted S-035 on September 14, 2005 (received September 16, 2005). The September 14, 2005 submission contained revised labeling for the package insert (PI) and immediate container and carton labeling as well as proposed labeling for new dosage strength presentations.

Review

I. Package Inserts

A. The PI in Y-010 (submitted February 28, 2005; received March 1, 2005) identified as "818 312 112" corresponds to the most recently approved labeling in S-034 (submitted on September 8, 2003; received September 9, 2003; amended with final printed labeling on March 26, 2004, received March 29, 2004, and approved April 21, 2004).

The sponsor submitted revisions to the PI in Y-035. The sponsor's proposed revisions are given in underlined type. The Division of Medial Imaging and Hematology Products proposed revisions to the sponsor's proposals follow the sponsor's iteration and are denoted by double underlines and cross outs.

1. CLINICAL TRIALS section:

a. Patients with Cancer and Acute Symptomatic Venous Thromboembolism subsection:

Sponsor's proposal:

(b) (4)

34 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_X_ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

(b) (4) [redacted] **The proposed color scheme for the new presentations are unacceptable.**

Conclusions

1. The following items were not submitted for revision: II.A-II.B., II.D.-E., III.A.-B., III.D.-E., IV.A.-B. and IV.D.-F.

2. The following items are editorial and acceptable: II. C.1.-4., II.F.1.-2., II.F.4.-13., III.C.2.-5., IV.C.1.-5., IV.G.1.-3., IV.G.4.a.-b., IV.G.4.d.-f. and IV.G.5.

3. The following items are not acceptable: II.C.5., II.F.3., II.G., III.C.1., III.F., IV.C.6., IV.G.4.c. and IV.H.

4. The sponsor should incorporate the proposed FDA revisions in item I. to the package insert.

5. The sponsor should propose revised color schemes for the new presentations that are sufficiently different from the already approved presentations to ensure that the presentations are not confused with each other. The proposed immediate container, blister labeling and carton labeling should not be approved.

Diane Leaman, B.S.
Regulatory Health Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Kyong "Kaye" Kang, Pharm. D.
Chief, Project Management Staff
Division of Medical Imaging and
Hematology Products
Center for Drug Evaluation and Research

Drafted: dl/February 21, 2006
Finalized: February 28, 2006
Filename: N20287S035RPMLblrev.doc

RPM LABELING REVIEW

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/s/

Diane V Leaman
3/3/2006 11:39:37 AM
CSO

Kyong Kang
3/3/2006 03:42:20 PM
CSO

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 20-287/S-035 Fragmin® (dalteparin sodium) Injection

Applicant: Pharmacia & Upjohn Company

Date of Application: March 16, 2004
Date of Receipt: March 17, 2004
Date of Filing Meeting: April 21, 2004
Filing Date: May 17, 2004

Indications requested: Extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer.

Type of Application: Full NDA _____ Supplement __X_____
(b)(1) __X_____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S
Resubmission after a withdrawal or refuse to file _no_____
Chemical Classification: (1,2,3 etc.)__3____
Other (orphan, OTC, etc.)___no_____

Has orphan drug exclusivity been granted to another drug for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid __2/25/04___ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES___X____ NO_____
User Fee ID#____4703_____
Clinical data? YES __X_____ NO _____ Referenced to NDA# _____
Date clock started after UN _N/A_____

User Fee Goal date: _1/17/05_____

Action Goal Date (optional) __N/A_____

- Does the submission contain an accurate comprehensive index? YES__
- Form 356h included with authorized signature? YES___

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? NA

- Patent information included with authorized signature? YES

- Exclusivity requested? NO If yes, _____years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? (b) (4)
  If no, for what ages and/or indications was a waiver and/or deferral requested:

- Field Copy Certification (that it is a true copy of the CMC technical section)? NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: IND 25,924

End-of-Phase 2 Meeting? Date: December 11, 2002 (agency letter)
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date: October 28, 2003
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? To be sent at a later date

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
N/A

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA

Advisory Committee Meeting needed? YES, date if known _____ NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? NO
  If no, did sponsor submit a complete environmental assessment? NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? N/A

- Establishment Evaluation Request (EER) package submitted? NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? N/A

If 505(b)(2), complete the following: N/A

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
N/A

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) N/A

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
N/A

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  N/A

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  N/A

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 21, 2004

TIME: 11:00-11:30 AM

LOCATION: Room 6B-45 (Parklawn)

APPLICATION: NDA 20-287/SE1-035; Fragmin® (dalteparin sodium, injection)

TYPE OF MEETING : Filing Meeting

MEETING CHAIR : Dr. Kathy Robie-Suh, Hematology Team Leader

MEETING RECORDER: Ms. Diane Moore, Regulatory Health Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISIONS:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Robert L. Justice, M.D., M.S., Director
Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Diane Moore, Regulatory Health Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-870)

Tien-Mien Chen, Ph.D., Biopharmaceutics Reviewer

Division of Biometrics II (DBII ; HFD-715)

Stella Grosser, Ph.D., Statistical Team Leader
Milton Fan, Ph.D., Statistician

Division of Scientific Investigations (GCPBI; HFD-46)

Khairy Malek, M.D., Medical Officer

BACKGROUND
Fragmin NDA 20-287 was approved December 22, 1994, for use in the prophylaxis of deep venous thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery and in patients undergoing abdominal surgery who are at risk for thromboembolic complications and for treatment of unstable angina and non-Q-wave myocardial infarction. The sponsor is submitting this efficacy supplement for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer.

MEETING OBJECTIVE:

To discuss the fileability of SE1-035, and potential review issues regarding the submission to convey to the sponsor in a regulatory letter.

Per reviewers, all parts in English, or English translation? YES__X___ NO___

1. CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES____X_____ NO_____
  A single pivotal study (CLOT study) was submitted for the application for complete treatment. Supportive studies were also submitted. About 600 patients were studied at 48 centers worldwide. Approximately 49% of the patients did not complete study treatment.
  Issues for the filing letter include:
  1. A single pivotal study (CLOT study) is submitted for the indication.
  2. The dropout rate in the CLOT study is large.
  3. In the CLOT study death, particularly death due to underlying cancer, during treatment appears significantly greater in the dalteparin group as compared to the oral anticoagulant group.

2. STATISTICAL – File __X_____ Refuse to file _____

- The endpoint is time to events

BIOPHARMACEUTICS – File __X_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ___X_____
- There are no Biopharm issues with this submission. Biopharm will review the labeling only.

PHARMACOLOGY – File __N/A_____ Refuse to file _____

- There are no Pharmacology issues with this submission.

CHEMISTRY – File __X_____ Refuse to file _____

- Establishment(s) ready for inspection? To Be Determined File__X___ Refuse to file _____
- There are no new strengths proposed for this indication. There are no chemistry issues.

REGULATORY CONCLUSIONS/ACTION ITEMS/DEFICIENCIES:

- The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- The supplement will have a 10-month review. Reviews will be due December 1, 2005. The PDUFA User Fee Goal Date is January 17, 2005.
- A consult will be sent to the Division of Drug Marketing, Advertising and Communication (DDMAC) for a review of the labeling.
- DGCDP will request DSI to inspect one or two sites for this supplemental application. Additional information regarding the number of patients enrolled per site, the number of patients randomized and treated, the number of patients completing treatment, the primary efficacy outcome, and major bleeding events will be requested from the sponsor.

- An Environmental Establishment Review (EER) will be requested by the CMC reviewer.
- A Filing Issues letter will be sent to the sponsor delineating the three potential review issues under Clinical (above).

_____
Regulatory Project Manager, HFD-180

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
4/29/04 10:09:13 AM
CSO

Kathy Robie-Suh
5/3/04 10:56:38 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-035

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 20-287 SUPPL # 035 HFD # 160

Trade Name Fragmin

Generic Name dalteparin sodium, injection

Applicant Name Pharmacia & Upjohn Company

Approval Date, If Known May 1, 2007

PART I - IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

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

NDA# 20-287 dalteparin sodium

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

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

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Study 98-FRAG-069 "Randomized Comparison of Low-Molecular Weight Heparin Versus Oral Anticoagulatin Therapy for Long-Term Anticoagulation in Cancer patients with Venous Thromboembolism (CLOT)"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

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

- Study 98-FRAG-069 (CLOT)

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

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 25,924	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

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

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Diane Leaman
Title: Regulatory Health Project Manager
Date: April 21, 2007

Name of Office/Division Director signing form: Rafel (Dwaine) Rieves, M.D.
Title: Acting Division Director, Division of Medical Imaging and Hematology Products, Office of Oncology Drug Products, Center for Drug Evaluation and Research

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Diane V Leaman
4/24/2007 05:37:59 PM

Rafel Rieves
4/24/2007 06:59:44 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : NDA 20-287 **Supplement Type (e.g. SE5): SE1** **Supplement Number: 035**

Stamp Date: March 17, 2004 **Action Date: January 17, 2005**

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

Applicant: Pharmacia and Upjohn Corporation **Therapeutic Class: S**

Indication(s) previously approved:

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

Number of indications for this application(s): 1

Indication #1: extended treatment of symptomatic venous thromboembolism (VTE (proximal DVT and /or PE) to prevent recurrent VTE in patients with cancer

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

- ☐ **Yes: Please proceed to Section A.**

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**

Reason(s) for partial waiver:

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

☐ **Other:**_____

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

Section C: Deferred Studies

Age/weight range being deferred:

Min X **kg**_____ **mo.** 3 **yr.**_____ **Tanner Stage**_____
Max X **kg**_____ **mo.**_____ **yr.** 18 **Tanner Stage**_____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): January 15, 2007

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

Section D: Completed Studies

Age/weight range of completed studies:

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

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 20-287/S-035
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

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

Indication #2: _____

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

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

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

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

Section D: Completed Studies

Age/weight range of completed studies:

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

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 10-287/S-035
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Diane V. Moore
1/10/05 05:57:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pfizer Inc.
Attention: Robert B. Clark
Vice President, US Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to the teleconference between Kathy Collins of your firm and the FDA on April 30, 2007. The purpose of the meeting was to discuss labeling for the Fragmin package insert (PI) in support of Supplement S-035.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: April 30, 2007

TIME: 1:30 PM- 2:00 PM

LOCATION: Diane Leaman's office Room 2360 (White Oak)

APPLICATION: NDA 20-287/S-035; Fragmin® (dalteparin sodium, injection)

INDICATION: Extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer

TYPE OF MEETING: Labeling Advice

MEETING CHAIR: Dr. Kathy Robie-Suh

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Medical Imaging and Hematology Products (DMIHP; HFD-160)

Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Andrew Dmytrijuk, M.D., Medical Officer
Diane Leaman, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pfizer

Kathy Collins, Regulatory Affairs

BACKGROUND:

On March 16, 2004 (received March 17, 2004), Pharmacia and Upjohn submitted NDA 20-287 Supplement S-035 (S-035) for a new indication for Fragmin for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The supplement was not approved on the first or second review cycle. Pfizer Inc. (agent for Pharmacia & Upjohn Company) resubmitted the supplement on February 28, 2007. Pfizer submitted revised labeling to the Division of Medical Imaging and Hematology Products (DMIHP) on April 27 and April 30, 2007. DMIHP requested this teleconference to discuss details from the sponsor's proposed labeling from April 30, 2007.

MEETING OBJECTIVE:

To convey labeling corrections to the Fragmin package insert (PI).

DISCUSSION POINTS:

- In the **DOSAGE AND ADMINISTRATION** section, **Extended Treatment of Venous Thromboembolism in Patients with Cancer** subsection, the word "symptomatic" should be inserted after the word "of" so that the title reads "**Extended Treatment of Symptomatic Venous Thromboembolism in Patients with Cancer**."

- In the **DOSAGE AND ADMINISTRATION** section, **Extended Treatment of Symptomatic Venous Thromboembolism in Patients with Cancer** subsection, in the first sentence that begins "In patients with cancer . . ." the word "symptomatic" should be inserted after the word "and" so that the sentence reads "In patients with cancer and symptomatic venous thromboembolism, the recommended dosing of FRAGMIN is as follows: for the first 30 days of treatment, administer FRAGMIN 200 IU/kg total body weight subcutaneously (s.c.) once daily.

- In the **CLINICAL TRIALS** section, **Patients with Cancer and Acute Symptomatic Venous Thromboembolism** subsection, in the second paragraph that begins "The median age . . ." please reorder the types of tumors in order of magnitude starting from the largest number to smallest number of tumors and ending with "other tumors" (even though "other tumors" is a larger group than two of the other tumor types).

- In the **CLINICAL TRIALS** section, **Patients with Cancer and Acute Symptomatic Venous Thromboembolism** subsection, in the fourth paragraph, first sentence that begins "In the intent-to-treat . . ." delete the second word "FRAGMIN" so that the sentence reads "In the intent-to-treat population that included all randomized patients, the primary comparison of the cumulative probability of the first VTE recurrence over the 6-month study period was statistically significant (p=0.0017) in favor of the FRAGMIN arm, with most of the treatment difference evident in the first month."

AGREEMENTS:

- Pfizer agreed to all of the above labeling revisions to the Fragmin PI.

CONCLUSIONS:

- Pfizer will draft a version of the Fragmin PI with the above revisions for submission to the NDA supplement.

ACTION ITEMS:

- Pfizer will submit a revised version of the Fragmin PI to the NDA supplement immediately.

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 Leaman
5/1/2007 02:39:15 PM

Pfizer, Inc
235 E. 42nd Street
New York, NY 10017

most recent sponsor labeling sub 4/30/07 Rec 4/30/07

facsimile transmittal

To: Diane Leaman Fax: 301-796-9909

From: Kathy Collins Date: 4/30/07

RE: Pages cover + 24

☒ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

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X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Pfizer, Inc
235 E. 42nd Street
New York, NY 10017

facsimile transmittal

To: Diane Leaman Fax: 301-796-9909

From: Kathy Collins Date: 4/30/07

RE: Pages cover + 24

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Worldwide Regulatory Affairs and Quality Assurance
Pfizer Inc
235 East 42nd Street 605/05/14
New York, NY 10017
Tel 212 733 5200 Fax 212 672 7605
Email kathy.collins@pfizer.com

Pfizer Global Pharmaceuticals

Kathy Collins
Director
Worldwide Regulatory Strategy

April 27, 2007

Rafel (Dwaine) Rieves, (Actg.) M.D., Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
c/o Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: **NDA 20-287/S-035— Fragmin® (dalteparin sodium injection)**
Response to Information Request Letter
Post-marketing Study Correspondence

Dear Dr. Rieves,

Reference is made to the Efficacy Supplement S-035 submitted March 16, 2004 for an indication for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to reduce the recurrence of VTE in patients with cancer. Reference is also made to the later submissions to this supplement including the March 14, 2006 non-approvable letter and Pfizer's February 28, 2007 response submission. Please refer to the FDA Information Request Letter dated April 24, 2007 and received via fax April 24, 2007 regarding the two post-marketing clinical studies we proposed in our February 2007 submission. Please refer also to the FDA revisions to the Information Request Letter sent and received via e-mail April 26, 2007 (D. Leaman, Regulatory Health Project Manager).

This letter is our commitment to perform the two post-marketing studies described below. Please note that all dates are as of the end of the month they occur in.

1. To evaluate efficacy and safety of dalteparin in pediatric cancer patients. Studies using dalteparin for venous thromboembolism (VTE) treatment in all age ranges of the pediatric population should be performed.

   Protocol Submissions: Within 6 months of the date of this letter.

THIS DOCUMENT CONTAINS CONFIDENTIAL AND/OR TRADE SECRET INFORMATION THAT IS DISCLOSED ONLY IN CONNECTION WITH THE LICENSING AND/OR REGISTRATION OF PRODUCTS FOR PFIZER INC OR ITS AFFILIATED COMPANIES. THIS DOCUMENT SHOULD NOT BE DISCLOSED OR USED, IN WHOLE OR IN PART, FOR ANY OTHER PURPOSE WITHOUT THE PRIOR WRITTEN CONSENT OF PFIZER INC

Study Start: Within 18 months of the date of this letter.
Final Report Submission: Within 36 months of the date of this letter.

2. To conduct a study to evaluate the safety and efficacy of dalteparin in cancer patients (both metastatic and non-metastatic) receiving extended treatment with dalteparin (>6 months) for prevention of new or recurrent symptomatic venous thromboembolism (VTEs), including subjects with renal impairment (including severe renal impairment).

Protocol Submissions: Within 6 months of the date of this letter.
Study Start: Within 18 months of the date of this letter.
Final Report Submission: Within 60 months of the date of this letter.

In addition, we will submit the final protocols to the IND associated with this NDA.

To facilitate timely review of this response, this submission is being sent in parallel via e-mail to Diane Leaman, Regulatory Health Project Manager, at diane.leaman@fda.hhs.gov.

If you have any further questions, please contact me via telephone at (212) 733-5200 or via fax at (212) 672-7605.

Sincerely,

Kathy Collins
Director, Worldwide Regulatory Strategy

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmacia & Upjohn Company	4/27/2007
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
212-573-3412	212-672-7807
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
235 East 42nd Street New York, NY 10017	Pfizer Inc 235 East 42nd Street New York, NY 10017

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 20-287

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Dalteparin sodium injection	FRAGMIN®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Oligo-Saccharides derived from heparin	Kabi 2165

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Parenteral: Solution for Injection	2500 IU, 5000 IU, 10,000 IU, 25,000 IU, 7500 IU	Injection

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER:

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION **Response to Information Request Letter Post-marketing Study Correspondence**

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(c)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER: **Response to Information Request Letter Post-marketing Study Correspondence**

CERTIFICATION

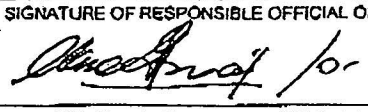
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	**Robert B. Clark** **Vice President, US Regulatory Strategy**	**4/27/2007**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
235 East 42nd Street, New York, NY 10017	**(212) 573-3412**

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
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Rockville, MD 20852-1448

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Document Information Page

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Application #(s):	NDA 20-287 S-035
Document Type:	NDA Telecon
COMIS Decision:	
Drafted by:	DL
Revised by:	
Initialed by:	A.Dmytrijuk, K.Robie-Suh, R.Rieves 4.26.07
Finaled:	April 27, 2007
Filename:	C:\Data\My Documents\FAXES\Pfizer\N20287S35FaxP4C2nd.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link this document to the incoming document the telecon concerns. If there is no such document, then link the document to the initial submission of the IND.

END OF DOCUMENT INFORMATION PAGE

The Fax begins on the next page.

Attachment

Dear Ms. Collins,

Please refer to your Supplemental New Drug Application (NDA) for Fragmin® (dalteparin sodium, injection). We note in your cover letter to your February 28, 2007 resubmission to NDA 20-287/S-035, your proposal for two post-marketing clinical studies. On April 24, 2007, we sent you a telefacsimile requesting that you put your Phase 4 Commitments in the format for these commitments. Please revise the study descriptions for the two studies as follows:

1. To evaluate efficacy and safety of dalteparin in pediatric cancer patients. Studies using dalteparin for venous thromboembolism (VTE) treatment in all age ranges of the pediatric population should be performed.

   Protocol Submissions: Within X months of the date of this letter.
   Study Start: Within Y months of the date of this letter.
   Final Report Submission: Within Z months of the date of this letter.

2. To conduct a study to evaluate the safety and efficacy of dalteparin in cancer patients (both metastatic and non-metastatic) receiving extended treatment with dalteparin (>6 months) for prevention of new or recurrent symptomatic venous thromboembolism (VTEs), including subjects with renal impairment (including severe renal impairment).

   Protocol Submissions: Within X months of the date of this letter.
   Study Start: Within Y months of the date of this letter.
   Final Report Submission: Within Z months of the date of this letter.

All submissions, including supplements, relating to these Postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol," "Postmarketing Study Final Report," or "Postmarketing Study Correspondence."

Protocols for the studies should be submitted for review. In addition, we will need the final protocols submitted to the IND associated with this NDA for review.

Please submit your agreement to perform these two studies in a letter to the NDA supplement.

Sincerely,

Diane Leaman, RPM
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: April 24, 2007

To: Kathy Collins	**From:** Diane Leaman
Company: Pfizer Global Pharmaceuticals	Division of Medical Imaging and Hematology Products
Fax number: (212) 338-1722	**Fax number:** (301) 796-9849
Phone number: (212) 733-5200	**Phone number:** (301) 796-1424

Subject: Phase 4 Commitment for postmarketing studies to NDA 20-287/S-035.

Total no. of pages including cover: 3

Comments: Wording format for Phase 4 (Postmarketing) protocols.

Document to be mailed: ☐ YES ☑ NO

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Attachment

Dear Ms. Collins,

Please refer to your Supplemental New Drug Application (NDA) for Fragmin® (dalteparin sodium, injection). We note in your cover letter to your February 28, 2007 resubmission to NDA 20-287/S-035, your proposal for two post-marketing clinical studies. One study will assess the safety of Fragmin administration for periods of time in excess of six months in patients with cancer and renal impairment including severe renal impairment. The second study will assess the safety and efficacy of Fragmin in pediatric patients with cancer who require anticoagulation. Associated protocol synopses have been provided which detail the study design, trial methodology, and enrollment criteria you would like to have considered for these studies.

In order to track Postmarketing studies, the studies should be submitted in the following format:

1. Study to assess the safety of Fragmin administration for periods in excess of six months in patients with cancer and renal impairment, including severe renal impairment.

   Protocol Submissions: Within X months of the date of this letter.
   Study Start: Within Y months of the date of this letter.
   Final Report Submission: Within Z months of the date of this letter.

2. Study to assess the safety and efficacy of Fragmin in pediatric patients with cancer who require anticoagulation.

   Protocol Submissions: Within X months of the date of this letter.
   Study Start: Within Y months of the date of this letter.
   Final Report Submission: Within Z months of the date of this letter.

All submissions, including supplements, relating to these Postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol," "Postmarketing Study Final Report," or "Postmarketing Study Correspondence."

In addition, we will need the final protocols submitted to the IND associated with this NDA for review.

Please submit your agreement to perform these two studies in a letter to the NDA supplement.

Sincerely,

Diane Leaman, RPM
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
4/24/2007 05:56:02 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

INFORMATION REQUEST LETTER

Pfizer Global Pharmaceuticals
Attention: Robert B. Clark
Vice President, US Regulatory Affairs
235 E. 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your March 16, 2005 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to your submission dated February 28, 2007.

We are reviewing the labeling in your submission and have the following comments and information requests.

Package Insert

Please find attached a draft revision of the Fragmin® (dalteparin sodium, injection) product labeling. We request you to incorporate the revisions in your package insert to your supplement as soon as possible. The draft is our preliminary text and important modifications of this text may be considered, if justified. Please correct any typographical and formatting errors.

General Labeling Comments

The colors for the proposed syringe strengths are similar to colors already used for existing syringe strengths. There is concern that the strengths with similar colors could easily be confused, leading to selection errors and resulting in the wrong dose being administered. We recommend that each syringe have a different, distinguishable color which may help practitioners differentiate between the Fragmin strengths and thus reduce the potential for selection errors and potential overdose.

Immediate container

The established name appears less prominent than the manufacturer name, "Esai Inc." Additionally, the font size and type (bold) of the manufacturer name competes with the

prominence of the proprietary name, Fragmin. Decrease the prominence of the manufacturer name so that it appears less prominent than the proprietary and established names.

Blister Labeling

The size and color of the font on the syringe blister backing are difficult to read. In particular, the (b) (4) colors are the most difficult to read. Revise the colors to improve readability or increase the font size and prominence accordingly. You may also wish to consider using black font for the text and using color blocking for the strength, similar to the presentation of the syringe strength on the container labels and carton labeling.

Carton labeling

The company name and corporate logo appear to be occupying more than 1/3 of the label. Decrease the size of the name and logos so that these have less prominence than the proprietary and established names.

We request a prompt written response in order to continue our evaluation of your NDA supplemental application.

If you have any questions, call Diane Leaman, Regulatory Health Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Alice Kacuba R.N., R.A.C.
Project Management Team Leader
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Attachment

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/s/

Alice Kacuba
4/19/2007 01:07:28 PM

Leaman, Diane V

m: cderdocadmin@cder.fda.gov
: Wednesday, April 18, 2007 3:34 PM
: Leaman, Diane V; Gantt, Sylvia; Riley, Bryan S
Subject: DFS Email - N 020287 SE1 035 AZ 28-Feb-2007 - Review (noted no comments - NAI)

Document room close out the following assignments:

	Personnel Code	Sup-Concur	St
N 020287 SE1 035 AZ 28-Feb-2007	66M	18-Apr-2007	NR

Document Type: Review (noted no comments - NAI)
Submission Description: No microbiology issues for labeling change

Author(s)/Discipline(s)

1. Stephen Langille, MICROBIOLOGIST

Signer(s)

1. Stephen Langille
   18-Apr-2007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pharmacia & Upjohn
Attention: Robert B. Clark
Vice President, U.S. Regulatory Strategy
Agent for Pharmacia & Upjohn Company
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

We acknowledge receipt on March 1, 2007 of your February 28, 2007 resubmission to your supplemental new drug application for Fragmin® (dalteparin sodium injection).

We consider this a complete, class 1 response to our March 14, 2006 action letter. Therefore, the primary user fee goal date is May 1, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted, in this submission, an agreement to submit a pediatric protocol for this application. Once the review of this application is complete we will notify you whether your proposal will fulfill the pediatric study requirement for this application.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Drug Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
3/9/2007 03:08:40 PM

Summary Minutes of the Oncologic Drugs Advisory Committee
September 6, 2006:

The summary minutes for the September 6, 2006 meeting of the Oncologic Drugs Advisory Committee were approved on September 13, 2006.

I certify that I attended the September 6, 2006 meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/	/s/
Johanna Clifford, M.Sc., RN Executive Secretary, ODAC	Maha Hussain, M.D., Acting Chair, ODAC

The meeting of the Oncologic Drugs Advisory Committee was held in the Maryland Ballroom, Hilton Washington DC/Silver Spring, Silver Spring, MD. Approximately 150 people were in attendance. The meeting was chaired by Maha Hussain, M.D.

The committee met to discuss new drug application (NDA) 20-287, proposed trade name FRAGMIN ® (dalteparin sodium) Injection, Pfizer, Incorporated, with proposed indication for the extended treatment of symptomatic venous thromboembolism (VTE), proximal deep vein thrombosis (DVT), and/or pulmonary embolism (PE) to reduce the recurrence of VTE in patients with cancer.

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
Ronald Bukowski, M.D., Maha Hussain, M.D. (Chair), David Harrington, Ph.D., Pamela Haylock, M.D., Alexandra Levine, M.D., Michael Perry, M.D., Maria Rodriguez, M.D.,

Oncologic Drugs Advisory Committee Consultants (voting):
Stephen George, D. Sc.; William Hiatt, M.D. (Cardio-Renal Committee); Karl Schwartz (patient representative); Michael Link, M.D., Gary Lyman, M.D., MPH.

Industry Representative (non-voting):
Antonio Grillo-Lopez, M.D.

Oncologic Drugs Advisory Committee Members Absent:
James Doroshow, M.D., S. Gail Eckhardt, M.D., Joanne Mortimer, M.D.

FDA Participants:
Richard Pazdur, M.D., Rafel Rieves, M.D.; Andrew Dmytrijuk, M.D.; Kathy Robie-Suh, M.D.; Jyoti Zalkikar, Ph.D.

Open Public Hearing Participants:
Frank Burroughs & Steve Walker, Abigail Alliance

The agenda proceeded as follows:

Sponsor Presentation	**Pfizer, Inc**
Introduction	Connie Newman, M.D. Therapeutic Area Head, CVMED Worldwide Regulatory Affairs and Quality Assurance
Background on VTE and Cancer	Craig Eagle, M.D., Senior Director Head of Worldwide Medical Oncology
CLOT Study Design & ITT Results	Agnes Y.Y. Lee, M.D., M.Sc., FRCPC Associate Professor, Medicine, McMaster University Hamilton Health Sciences Henderson Hospital Hamilton, ON
CLOT Study Further Analyses	Craige Eagle, M.D.
Conclusion	Craig Eagle, M.D.

FDA Presentation
FDA Review of Clinical Data:
Fragmin for treatment of VTE
in cancer patients

NDA 21-986
Amdrew Dmytrijuk, M.D., Medical Officer
Division of medical Imaging and Hematology
OODP, CDER, FDA

Questions from the Committee

Open Public Hearing

Questions to the Committee

MEETING QUESTIONS

1. Safety: The FDA review of the CLOT study cited a potentially important mortality safety signal related to the study drug discontinuation findings. Discontinuation of the assigned study drug due to death was twice as common among patients receiving Fragmin as it was among patients receiving OAC. The cause for this imbalance is unclear and not explained by findings within the CLOT study database. For example, the database did not show an excess in fatal hemorrhage among patients receiving Fragmin. Post-hoc hypotheses, such as the possibility of informative censoring, have been proposed to account for the study drug discontinuation finding. Regarding the excessive number of Fragmin discontinuations due to death:

VOTE: Do you regard the study drug discontinuation due to death finding as sufficient to preclude the approval of the application until the issue is resolved with additional clinical studies?

Yes = 0 ***No = 12***

Overall the committee felt that the explanation provided for deaths and study drug discontinuation in both arms of the study was sufficient, although misleading, due to coding issues, differing patient management in either arm, etc. The committee felt that based on this aspect alone (study drug discontinuation), ruling out approval was not appropriate.

2. Efficacy: In order to rely on a single clinical study for definitive evidence of safety and efficacy, the primary efficacy endpoint result should be a robust finding. Special considerations in evaluating the CLOT study's primary endpoint result include the open label nature of the study, the differing anticoagulation management between the study groups, the endpoint's competing risk with mortality, possible bias in VTE symptom detection and inconsistencies in exploratory analyses of the primary endpoint result.

VOTE: Considering these endpoint limitations, does the CLOT study provide substantial evidence of effectiveness?

Yes = 12 ***No = 0***

The committee voted unanimously that despite the endpoint limitations, the study provided substantatial evidence of effectiveness. Although there were multiple reservations noted. Specifically, that the study has not proved the long-term use (additional 5 months) of the product and that the study could have been "cleaner" with respect to anticipation of the high mortality rate and more standardization of VTE ascertainment between the study groups.

3. Safety and Efficacy: If you provide favorable responses to the preceding safety and efficacy questions ("no" to safety question 1 and "yes" to efficacy question 2):

VOTE: Does the totality of the CLOT study's safety and efficacy results provide a benefit to risk relationship sufficient to warrant approval of this supplemental marketing application?

Yes = 12 ***No = 0***

Although the committee felt that the data presented does, in fact, warrant concern by the committee and the FDA, with further explanation of the death due to the disproportionate "on treatment" censorship of the deaths, the committee felt comfortable with the overall death curves presented in the data and thus overwhelming felt that the evidence provided in the CLOT study's result did warrant approval of the product.

4. Label Considerations: The CLOT study included predominantly patients with advanced (metastatic) cancer. Exploratory subset analyses did not support an apparent treatment effect within the subsets of patients with hematological malignancies or patients with non-metastatic cancer.

a. VOTE: If marketing approval is recommended, should the product label limit the indicated patient population to a subset of "cancer patients" (for example, only patients with metatstatic, non-hematologic cancer)?

Yes = 2 ***No = 10***

The committee felt that there was not enough evidence to limit the patient populations in the labelling to those with particular malignancies, expressing some concern with the subgroup analysis which they felt were difficult to interpret and not really valid. In addition, the committee expressed an interest in seeing post marketing data in the specific categories of patients with more limited disease.

b. DISCUSSION: If you vote to limit the indicated patient population, please discuss any important patient population limitations.

5. Additional Clinical Studies: The CLOT study was conducted among "cancer patients" and included predominantly patients with advanced (metastatic cancer). Limitations in the study design were cited above.

DISCUSSION: If marketing approval is not recommended, please describe the types of clinical data the sponsor should submit to support approval, including any important study design considerations and the potential need for study of patients without cancer or the study of specific cancer patient populations.

The committee did not address this question.

The meeting adjourned at approximately 5:00 p.m.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pfizer Inc.
Attention: Robert B. Clark
Vice President, US Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to the teleconference between representatives of your firm and the FDA on June 13, 2006. The purpose of the meeting was to discuss the CLOT study.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: June 13, 2006

TIME: 3:00 PM- 3:15 PM

LOCATION: Conference Room 1313 (White Oak)

APPLICATION: NDA 20-287/S-035; Fragmin® (dalteparin sodium, injection)

INDICATION: Extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer

TYPE OF MEETING: Clinical Advice

MEETING CHAIR: Dr. Rafel Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Office of Oncology Drug Products (OODP)

Karen Weiss, M.D., Deputy Director

Division of Medical Imaging and Hematology Products (DMIHP; HFD-160)

Rafel Rieves, M.D., Deputy Director
George Shashaty, M.D., Medical Officer
Andrew Dmytrijuk, M.D., Medical Officer
Diane Leaman, Regulatory Health Project Manager
Lynn Henley, Regulatory Project Manager

Office of Biostatistics

Dr. Jyoti Zalkikar, Team Leader
Dr. Satish Misra, Statistician

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pfizer

Craig Eagle MD, Group Leader, WW Medical Oncology
Connie Newman, M.D., Regulatory therapeutic Area Leader Cardiovascular Products
William Spalding, M.S., Associate Director, Biometrics
Michael Gaffney, Ph.D., Senior Director, Statistical Research & Consulting
Andrea Kollath DVM, Regulatory Lead Fragmin
Fred Rickles, M.D., F.A.C.P., CLOT Steering Committee

Mark Talsey, Executive Director, Regulatory
Viviana Bozon, Associate Director, Medical

Consultant:

Agnes Lee, M.D., M.Sc., F.R.C.P., (C), Associate Professor, Department of Medicine, Mc Master University, Hematology & Thromboembolism, Hamilton Health Sciences, Hamilton, Ontario, Canada

BACKGROUND:

On March 16, 2004 (received March 17, 2004), Pharmacia and Upjohn submitted NDA 20-287 Supplement S-035 (S-035) for a new indication for Fragmin for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The NDA was issued an approvable action on January 14, 2005. Pharmacia and Upjohn resubmitted the supplement on September 14, 2005 (received September 15, 2005). On January 24, 2006, the DMIHP sent Pharmacia and Upjohn a letter requesting additional information for S-035. An additional request for information was sent to the sponsor on January 30, 2006, by telefacsimile. On March 14, 2006, DMIHP sent Pharmacia & Upjohn a "Not Approvable" letter for S-035. On April 12, 2006 (received April 13, 2006) Pfizer (agent for Pharmacia & Upjohn) requested a meeting to discuss the not approvable action received for S-035. DMIHP granted Pfizer a meeting for June 13, 2006. DMIHP also agreed to allow Pfizer to present any additional information they could on their interpretation of the CLOT trial results at a teleconference scheduled for May 2, 2006. On April 24, 2006, Pfizer submitted background information for the May 2, 2006 teleconference. On May 1, 2006, Pfizer sent, via e-mail, an additional table and graphs for reference at the May 2, 2006 teleconference. On May 2, 2006, Pfizer met with DMIHP for further discussion regarding the interpretation of the CLOT study's safety and efficacy results. On June 1, 2006, DMIHP sent Pfizer (via telefacsimile) the Agency responses to the sponsor's questions posed in the May 22, 2006 background package (see below). On June 9, 2006, DMIHP called Pfizer to inform the sponsor that the Division has decided to take the discussion of the data from the CLOT study to an Advisory Committee. On June 12, 2006, Pfizer sent DMIHP a response to the May 2, 2006 meeting minutes (see attached).

MEETING OBJECTIVE:

To discuss the status of the CLOT study.

DISCUSSION POINTS:

The following are the sponsor questions from the May 22, 2006 background package from Pfizer followed by the FDA responses provided in the June 1, 2006 telefacsimile.

Question 1.
The CLOT trial provides definitive evidence of the safety of dalteparin in patients with cancer as explained in the Briefing Document of May 22, 2006.

Does the Agency agree?

FDA Response:
No. The issue of competing risk prevents the conclusion of definitive evidence of safety of dalteparin. This confounding effect of competing risk is inherent in the design of the trial and in the patient population selected.

Question 2.
The sponsor believes that the estimated hazard ratio for VTE is an unbiased estimate of the significant benefit of dalteparin relative to OAC.

Does the Agency agree?

FDA Response:
No. The issue of competing risk also confounds the estimated hazard ratio for VTE. (See response to Question 1).

Question 3.
The post approval study Pfizer proposes to conduct is adequate and meets FDA requirements.

Does the Agency agree?

FDA Response:
We have concerns regarding the proposed study design and development program. We would like to discuss the clinical development program with you, including plans for the next clinical study.

The sponsor presented their summary of the CLOT study and their disagreements with the interpretation of the study results by DMIHP (see attached).

AGREEMENTS: none

CONCLUSIONS:

- The Agency will be presenting issues from the Fragmin CLOT study at a September 2006 Oncology Advisory Committee Meeting.
- Pfizer agrees to participate in the Advisory Committee Meeting.

ACTION ITEMS:

- The Agency will be contacting Pfizer with details of the Advisory Committee meeting in the near future.

UNFINISHED ITEMS: none

Pfizer Inc
235 East 42nd Street 605/5/22
New York, NY 10017
Tel 212 733 0466 Fax 212 857 3558
Andrea.F.Kollath@Pfizer.com



Pfizer Global Pharmaceuticals
Andrea Kollath D.V.M.
Regulatory Liaison Director
Worldwide Regulatory Affairs & Quality Assurance

June 12, 2006

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center of Drug Evaluation and Research
Food and Drug Administration
Document Control Room 8B45
10903 New Hampshire Avenue
Silver Spring, MD 20913

RE: NDA 20-287 – Fragmin ® (dalteparin sodium)

GENERAL CORRESPONDENCE – RESPONSE TO MAY 2, 2006 MEETING MINUTES

Dear Ms. Leaman,

Reference is made to the written correspondence received via facsimile on June 5, 2006 that contained the official minutes of the meeting conducted with Pfizer and FDA on May 2, 2006. This meeting was conducted between Pfizer and DMHP to discuss the interpretation of the CLOT trial regarding safety and efficacy results. Pursuant to our review of these minutes today, we are providing the following clarifications regarding the agreements and conclusions detailed in your correspondence:

AGREEMENTS:

- Pfizer and the Agency agree that the "on treatment" mortality analysis was biased by informative censoring. The Agency agrees that the difference in "on treatment" mortality may be due to informative censoring related to underlying disease management.

  Pfizer respectfully disagrees that when the informative censoring concepts are taken into account with respect to study efficacy results that there is no demonstration of efficacy.

Pfizer also disagrees with the statement that the study is inconclusive with regard to safety and efficacy.

Pfizer sent a written response to FDA regarding the competing risk in the CLOT study and a discussion with regard to interpretation of the primary endpoint. Please refer to our general correspondence submitted on May 8, 2006.

CONCLUSIONS:

- Pfizer respectfully disagrees that these conclusions were mutually reached as a result of the teleconference.

  Pfizer's position is that informative censoring only applies to the "on treatment" analysis. ITT mortality analysis eliminates informative censoring bias. The ITT mortality analysis showed no difference between the two treatment arms.

  Censoring due to mortality does not invalidate the significant benefit of dalteparin on VTE as shown in Pfizer's response of May 8, 2006.

  Pfizer believes that the results of the CLOT study data presented in ITT analyses are conclusive.

  During the teleconference there was no discussion of the need for additional studies.

Should you have any questions regarding the clarifications provided in this correspondence please contact me by phone (212) 733-0466) or by fax (212) 857-3558.

Sincerely,

Andrea Kollath D.V.M.

27 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Diane V Leaman
6/28/2006 04:51:34 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: June 1, 2006

To: Andrea Kollath	**From:** Diane Leaman
Company: Pfizer Global Pharmaceuticals.	Division of Medical Imaging and Hematology Products
Fax number: 212-857-3558	**Fax number:** (301) 796-9849
Phone number: (212) 733-0466	**Phone number:** (301) 796-1424

Subject: Supplement-035 and the CLOT study.

Total no. of pages including cover: 3

Comments: Attached are the FDA responses to your questions regarding your Type C clinical meeting which you posed in your May 22, 2006, submission. Your questions are in italic type. Our responses are in bold type. You have the option of canceling our meeting scheduled for June 13, 2006, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss or reach agreement on such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible whether you are canceling the meeting.

Diane Leaman, RPM
Division of Medical Imaging and Hematology Products

Document to be mailed: ☐ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Question 1.
The CLOT trial provides definitive evidence of the safety of dalteparin in patients with cancer as explained in the Briefing Document of May 2, 2006.

Does the Agency agree?

FDA Response:
No. The issue of competing risk prevents the conclusion of definitive evidence of safety of dalteparin. This confounding effect of competing risk is inherent in the design of the trial and in the patient population selected.

Question 2.
The sponsor believes that the estimated hazard ratio for VTE is an unbiased estimate of the significant benefit of dalteparin relative to OAC.

Does the Agency agree?

FDA Response:
No. The issue of competing risk also confounds the estimated hazard ratio for VTE. (See response to Question 1).

Question 3.
The post approval study Pfizer proposes to conduct is adequate and meets FDA requirements.

Does the Agency agree?

FDA Response:
We have concerns regarding the proposed study design and development program. We would like to discuss the clinical development program with you, including plans for the next clinical study.

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/s/

Diane V Leaman
6/1/2006 12:50:30 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pfizer Inc.
Attention: Robert B. Clark
Vice President, US Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to the teleconference between representatives of your firm and the FDA on May 2, 2006. The purpose of the meeting was to discuss Pfizer's interpretation of the data from the CLOT study in regard to the safety signal seen in the advanced cancer patient population in support of Supplement S-035.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: May 2, 2006

TIME: 1:30 PM- 3:00 PM

LOCATION: Conference Room 2376 (White Oak)

APPLICATION: NDA 20-287/S-035; Fragmin® (dalteparin sodium, injection)

INDICATION: Extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer

TYPE OF MEETING: Clinical Advice

MEETING CHAIR: Dr. Rafel Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Office of Oncology Drug Products (OODP)

Richard Pazdur, M.D., Director,
Karen Weiss, M.D., Deputy Director

Division of Medical Imaging and Hematology Products (DMIHP; HFD-160)

Rafel Rieves, M.D., Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Andrew Dmytrijuk, M.D., Medical Officer
Diane Leaman, Regulatory Health Project Manager

Office of Biostatistics

Dr. Jyoti Zalkikar, Team Leader
Dr. Satish Misra, Statistician

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pfizer

Craig Eagle MD, Group Leader, WW Medical Oncology
Viviana Bozon MD, Associate Director, WW Medical Oncology
Connie Newman MD, Regulatory Therapeutic Area Leader Cardiovascular Products
William Spalding MS, Associate Director, Biometrics
Michael Gaffney PhD, Senior Director, Statistical Research & Consulting
Andrea Kollath DVM, Regulatory Lead Fragmin

Consultants:

Agnes Lee MD, MSc, FRCP (C), Associate Professor, Department of Medicine. Hematology & Thromboembolism Hamilton Health Sciences, Hamilton, Ontario, Canada

(b) (4)

[redacted]

BACKGROUND:

On March 16, 2004 (received March 17, 2004), Pharmacia and Upjohn submitted NDA 20-287 Supplement S-035 (S-035) for a new indication for Fragmin for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The NDA was issued an approvable action on January 14, 2005. Pharmacia and Upjohn resubmitted the supplement on September 14, 2005 (received September 15, 2005). On January 24, 2006, the DMIHP sent Pharmacia and Upjohn a letter requesting additional information for S-035. An additional request for information was sent to the sponsor on January 30, 2006, by telefacsimile. On March 14, 2006, DMIHP sent Pharmacia & Upjohn a "Not Approvable" letter for S-035. On April 12, 2006 (received April 13, 2006) Pfizer (agent for Pharmacia & Upjohn) requested a meeting to discuss the not approvable action received for S-035. DMIHP granted Pfizer a meeting for June 13, 2006. DMIHP also agreed to allow Pfizer to present any additional information they could on their interpretation of the CLOT trial results at a teleconference scheduled for May 2, 2006. On April 24, 2006, Pfizer submitted background information for the May 2, 2006 teleconference. On May 1, 2006, Pfizer sent via e-mail an additional table and graphs for reference at the May 2, 2006 teleconference (see attached).

MEETING OBJECTIVE:

To open a discussion between Pfizer and DMIHP on the interpretation of the CLOT trial regarding safety and efficacy results.

DISCUSSION POINTS:

- The sponsor presented their interpretation of the CLOT study results.

- The Division noted that the CLOT study was an unblinded study in which an injectable product was compared to an oral product. Hence, the administration regimens for the two study products may have confounded the study results. The study analyzed the time to recurrent VTE as well as mortality up to one year in patients with cancer. The primary endpoint of thrombotic events was potentially confounded by the competing event of death (dropout rate due to death in the cancer population). Exploratory analyses indicated a higher rate of discontinuation of the study drug due to death in the Fragmin arm than in the comparator arm of the study.

- The sponsor stated that "on treatment" mortality analysis was flawed because of informative censoring. Extending the number of days that would be considered "on treatment" shows that the hazard ratio for death is similar between the study groups. The sponsor noted that this observation invalidates the meaningfulness of the "on treatment" mortality analyses.

- The Agency expressed concern about the lack of robustness within the study findings. The Agency noted that an analysis that considers the primary efficacy endpoints as the composite of "time to first VTE" or "death" is a better analysis than an analysis that has an endpoint without death. The time to the first recurrence of VTE or death at six months shows no significant efficacy difference between the two arms.

- The Division asked the sponsor why discontinuations due to death were not mentioned in the New England Journal of Medicine article. The sponsor noted that the publication was developed by Dr. Lee and the results were presented in a manner that the authors regarded as appropriate.

- General aspects of informative censoring and competing risk concepts were discussed.

AGREEMENTS:

- The Agency agrees that informative censoring issues may have occurred in this open label trial. The Agency agrees that the safety issues in the study results may be attributable to biases from informative censoring in the study analyses. However, when the informative censoring concepts are taken into account with respect to the study efficacy results (i.e., death considered in the primary efficacy endpoints along with VTE) there is no demonstration of efficacy. The Agency regards the study as inconclusive with respect to safety and efficacy.

- At the request of Dr. Pazdur, Pfizer agreed to send to FDA a written explanation regarding competing risks in the CLOT trial and a discussion with regard to interpretation of the primary endpoint.

CONCLUSIONS:

- Informative censoring in the CLOT study may have impacted the safety issues with regard to mortality. The study data are inconclusive.

- The open label study design may have allowed for bias in the differential handling of patients in the two treatment groups, especially with respect to discontinuation of study drugs.

- The informative censoring may have affected both safety and efficacy parameters in the study.

- The Division cannot reach a conclusion regarding the safety and efficacy assessed in the CLOT study. Additional studies are needed. For example, a study in non-cancer patients needs to be performed to better evaluate the possible effect on death and the overall risk/benefit relationship. Study design should incorporate measures to minimize bias in patient management.

- The Agency requests that Pfizer submit a discussion of the competing risks and interpretation of the primary endpoint to the NDA by May 8, 2006

ACTION ITEMS:

- Pfizer will draft a statistical explanation showing that competing risk/informative censoring does not invalidate efficacy. This response will be submitted to the NDA on Monday May 8, 2006.

UNFINISHED ITEMS:

- The FDA will address the sponsor's questions at the meeting scheduled for June 13, 2006.
- Pfizer will comment about the NEJM paper at the face-to-face meeting scheduled for June 13, 2006.

POST-MEETING ADDENDUM:

On May 8, 2006, received May 9, 2006, Pfizer submitted their explanation regarding competing risks and informative censoring in regard to the CLOT study to NDA 20-287/S-035.

Although more patients in the dalteparin arm than in the OAC arm discontinued treatment due to death (16.6% vs 7.2%), in the vast majority of the cases the reason for death was related to the underlying cancer. Only 4 dalteparin patients and 7 OAC patients died for non-cancer-related reasons. Fatal PE was the reason for death in 3 dalteparin- (#102-003; #402-010, and #801-027) and 5 OAC-treated patients (#402-013, #504-007, #507-001, #507-011, and #702-001). Another dalteparin patient died due to a fatal PE the day after discontinuation of therapy (#102-022). The reported reason for discontinuation was confirmed acute PE. Fatal hemorrhage occurred in 1 patient treated with dalteparin (#701-004, hemoptysis) and in none of the patients receiving OAC. The 2 remaining OAC patients (#102-055, and #203-004) died due to sepsis and hypothermia, respectively.

Adverse events causing interruption of treatment occurred similarly in the 2 arms (5.0% and 5.7% in the dalteparin and OAC group, respectively).

No important differences were observed between the 2 groups in the frequency of the other reasons for discontinuation.

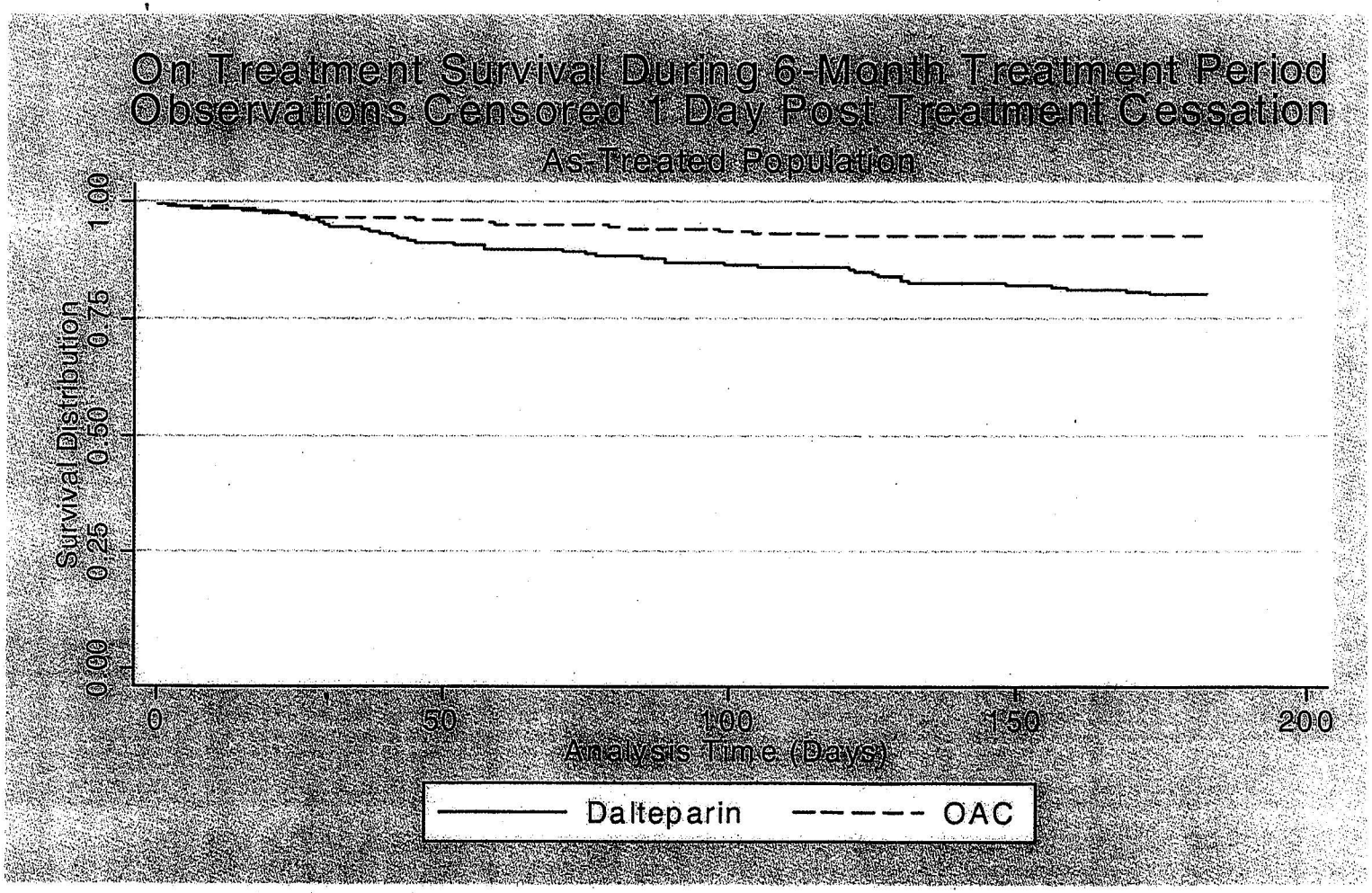
Table 12. Reasons for Discontinuation (As-treated Population)

	Dalteparin N=338		OAC N=335		Total N=673	
	N	%	N	%	N	%
Patients who completed treatment	180	53.3	163	48.7	343	51.0
Patients who discontinued	158	46.7	172	51.3	330	49.0
Death	56	16.6	24	7.2	80	11.9
Underlying cancer	52	15.4	17	5.1	69	10.3
Fatal PE	3	0.9	5	1.5	8	1.2
Fatal bleeding	1	0.3	0	0.0	1	0.1
Other	0	0.0	2	0.6	2	0.3
Confirmed acute VTE	21	6.2	47	14.0	68	10.1
DVT	12	3.6	35	10.4	47	7.0
PE	7	2.1	10	3.0	17	2.5
CVT of upper limb	2	0.6	2	0.6	4	0.6
Contraindication to anticoagulation	12	3.6	25	7.5	37	5.5
Bleeding	10	3.0	19	5.7	29	4.3
Other	1	0.3	6	1.8	7	1.0
Missing	1	0.3	0	0.0	1	0.1
Adverse event	17	5.0	19	5.7	36	5.3
Abnormal bloodwork	4	1.2	4	1.2	8	1.2
Abnormal investigation results	1	0.3	1	0.3	2	0.3
Patient decision / withdrawal of consent	20	5.9	14	4.2	34	5.1
Other	27	8.0	38	11.3	65	9.7
Underlying cancer	17	5.0	21	6.3	38	5.6
Investigator decision	1	0.3	5	1.5	6	0.7
Patient unable to swallow	0	0.0	4	1.2	4	0.6

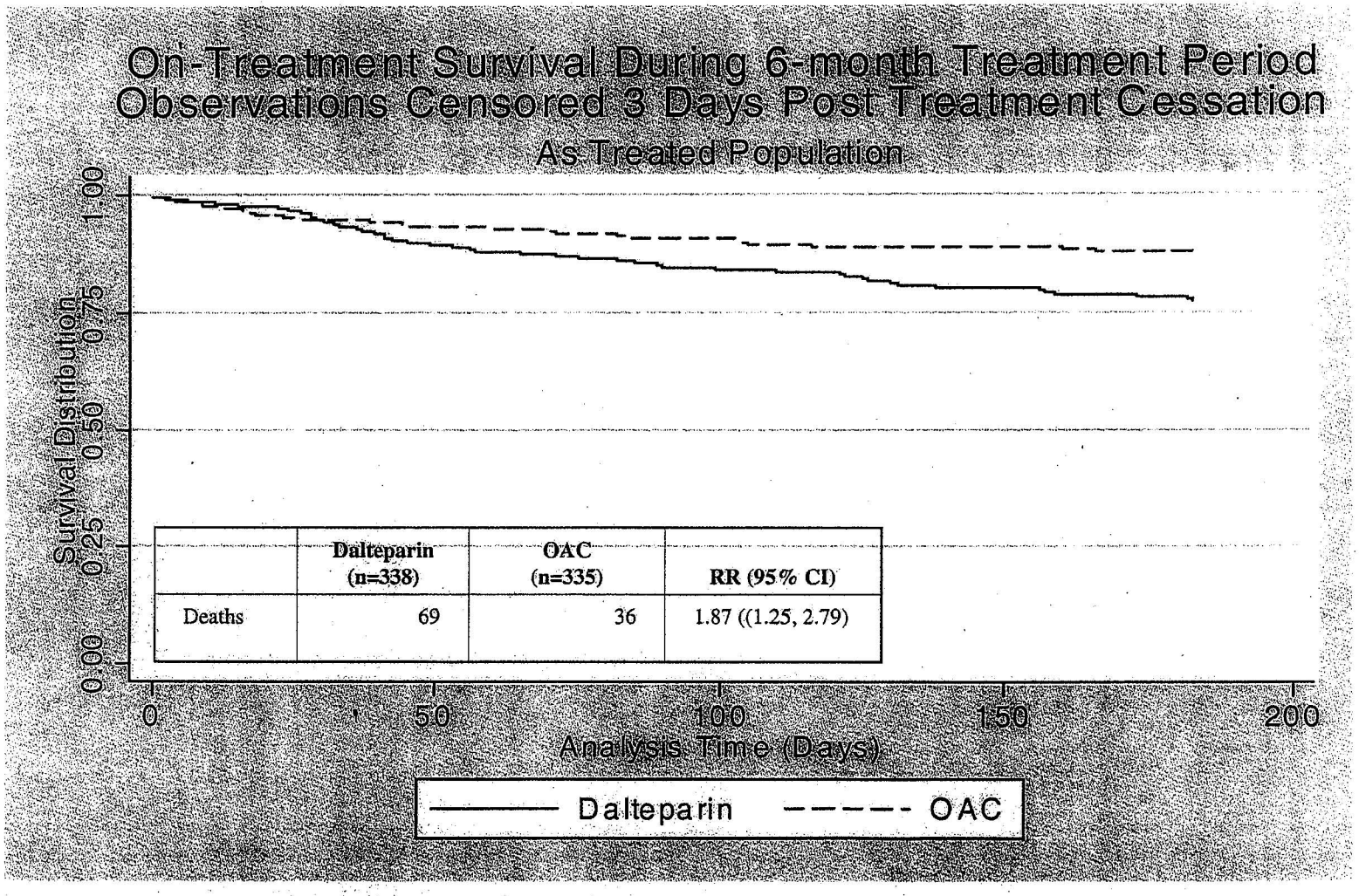
Abbreviations: CVT = central venous thrombosis; DVT = deep vein thrombosis; OAC = oral anticoagulant; PE = pulmonary embolism; VTE = venous thromboembolic event
Source: Table T1.4, Appendix 3.1.1, 3.1.2, and 3.6.3

Appendix 3.1.1 contains a listing of subjects that discontinued from the study.

1 day lag time

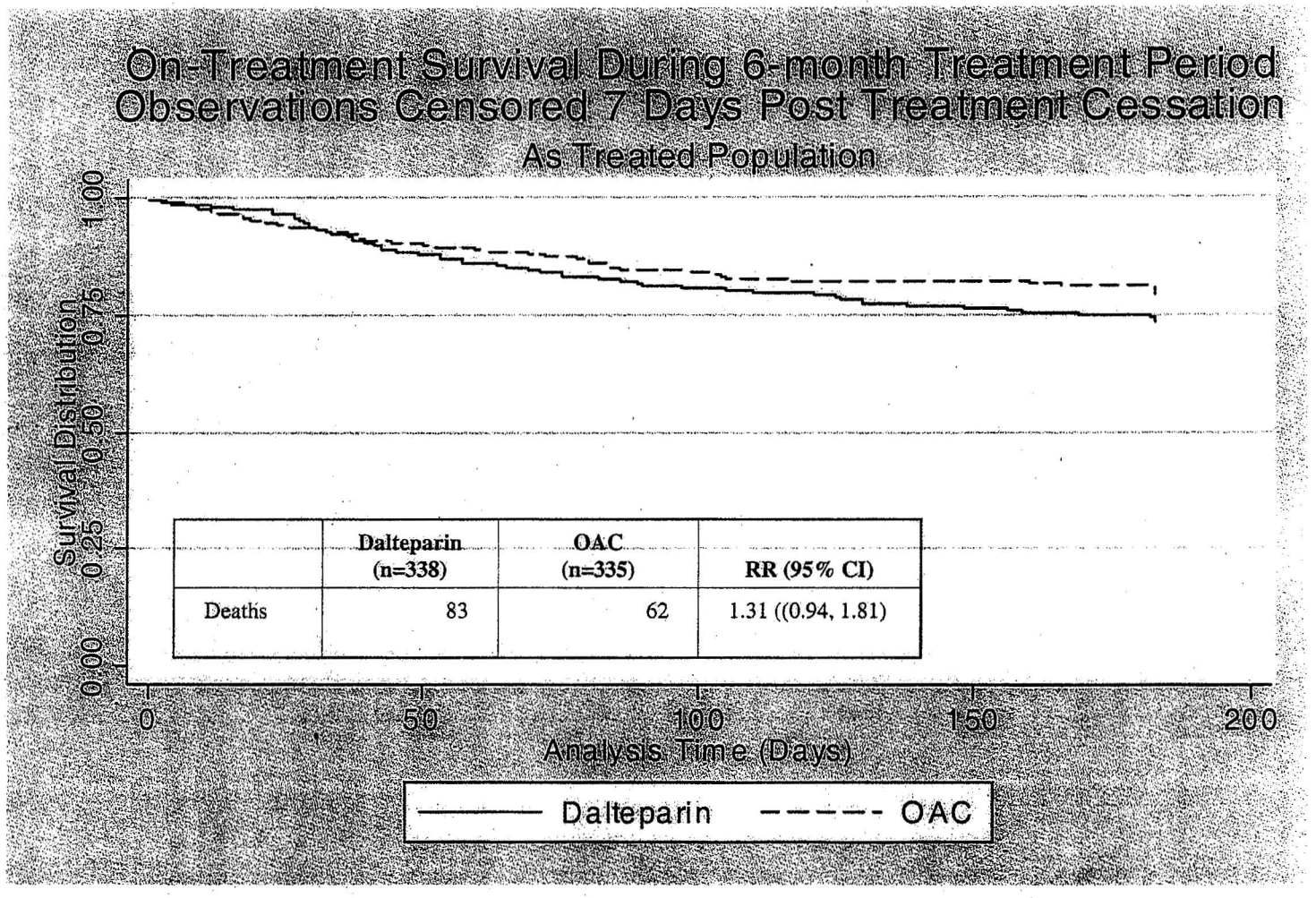


3 day lag time



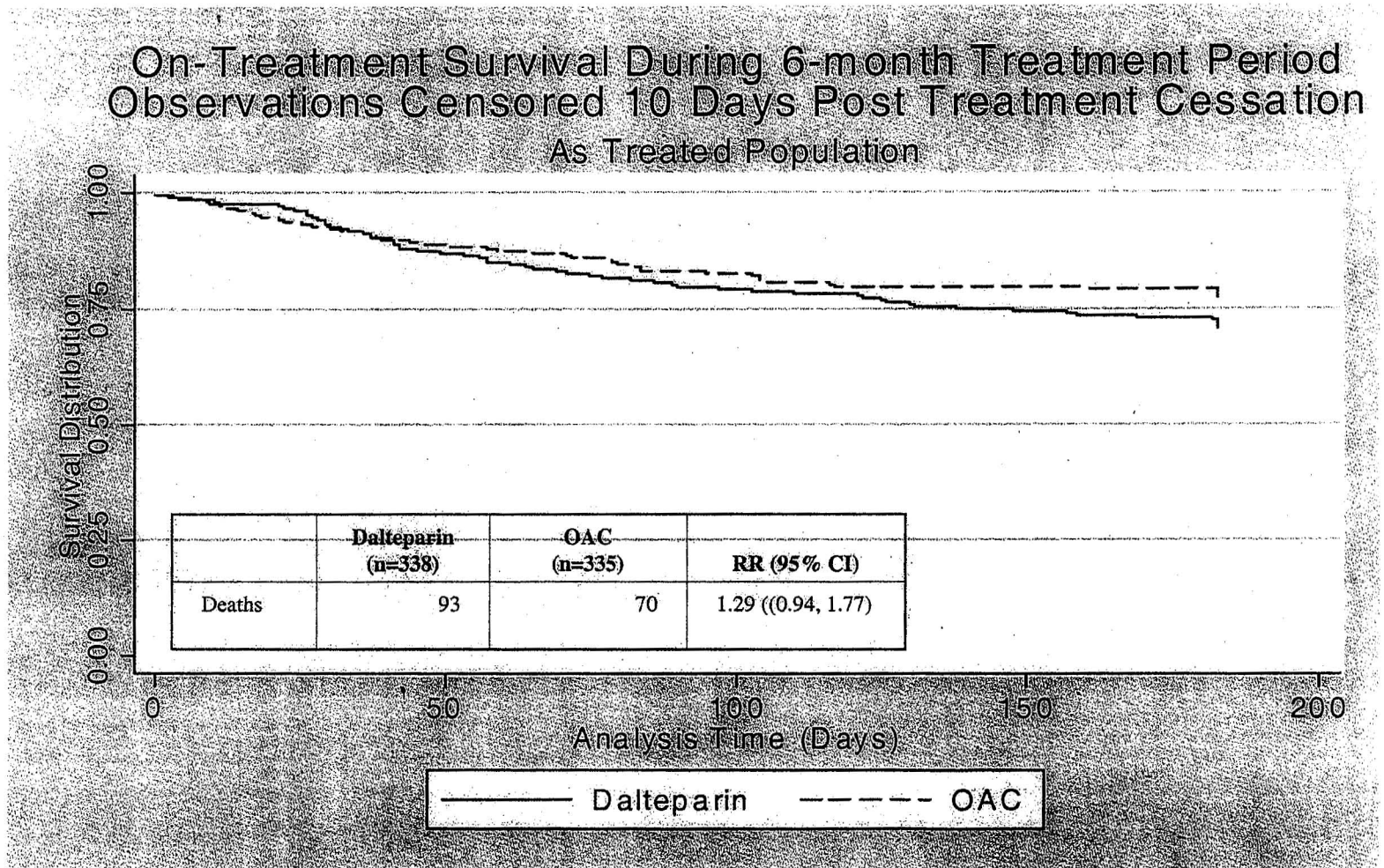
	Dalteparin (n=338)	OAC (n=335)	RR (95% CI)
Deaths	69	36	1.87 ((1.25, 2.79)

7 day lag time



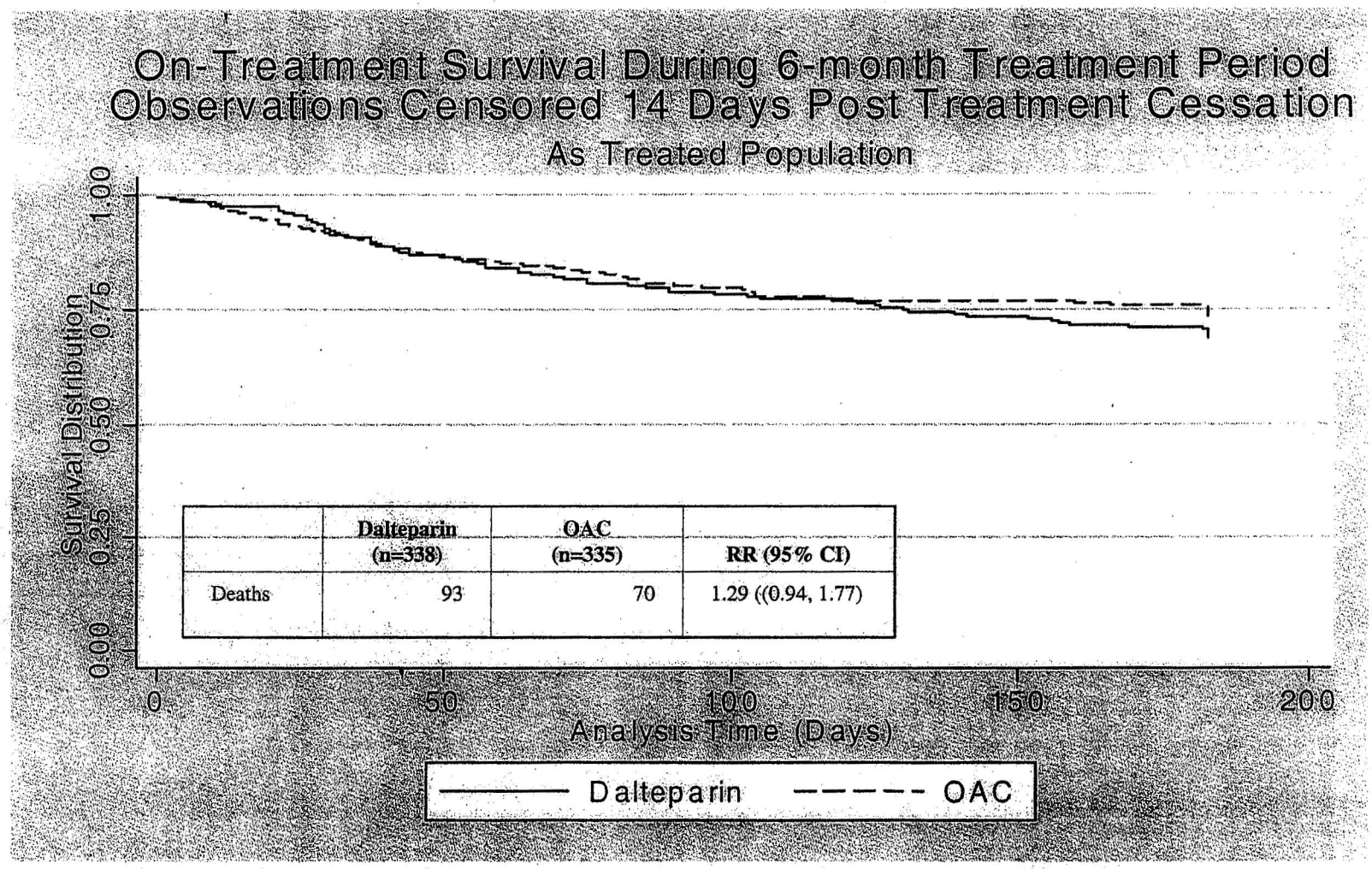
	Dalteparin (n=338)	OAC (n=335)	RR (95% CI)
Deaths	83	62	1.31 ((0.94, 1.81)

10 day lag time

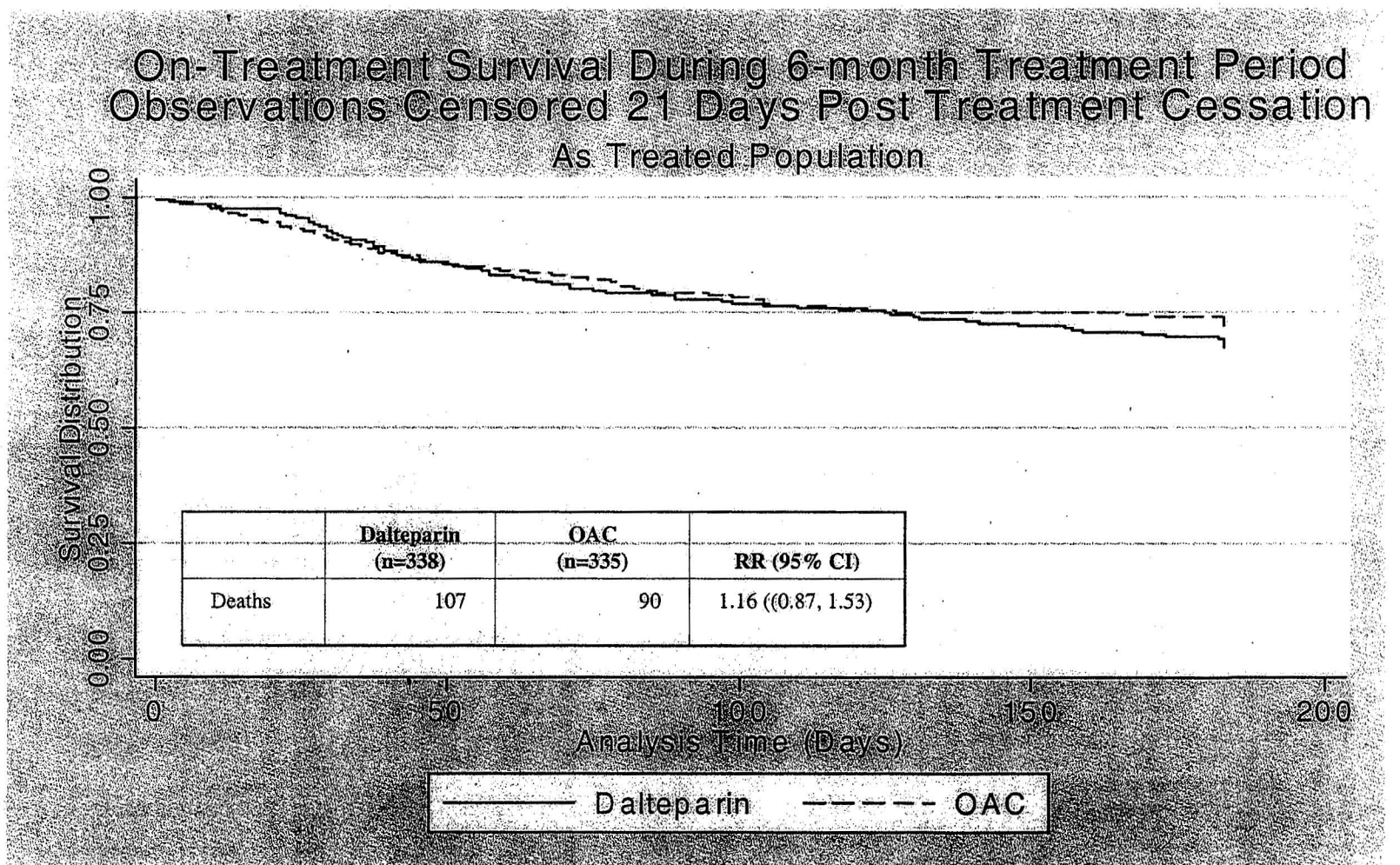


	Dalteparin (n=338)	OAC (n=335)	RR (95% CI)
Deaths	93	70	1.29 ((0.94, 1.77)

14 day lag time

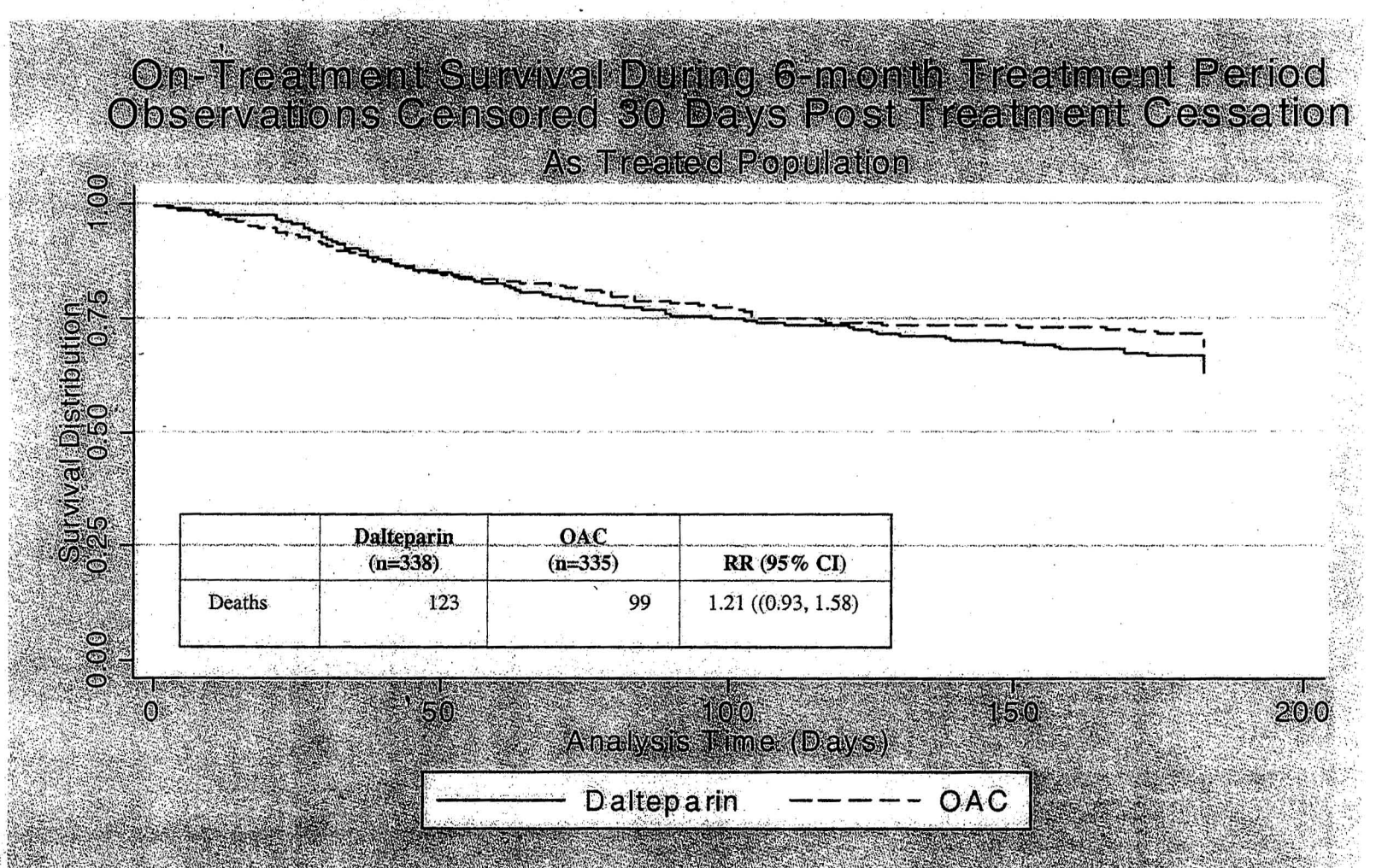


21 day lag time



	Dalteparin (n=338)	OAC (n=335)	RR (95% CI)
Deaths	107	90	1.16 ((0.87, 1.53)

30 day lag time



	Dalteparin (n=338)	OAC (n=335)	RR (95% CI)
Deaths	123	99	1.21 ((0.93, 1.58)

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 Leaman
6/1/2006 12:38:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pfizer Inc.
Attention: Robert B. Clark
Vice President, US Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your Investigational New Drug Application (IND)/New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to your April 12, 2006, correspondence, received April 14, 2006, requesting a meeting to discuss Supplement S-035 and the Agency action letter dated March 14, 2006.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: June 13, 2006
Time: 2:30 – 4:00 PM
Location: Room 1313, Building 22, White Oak Campus, 10903 New Hampshire Ave, Silver Spring, MD 20913

CDER participants: Dr. Richard Pazdur
Dr. Karen Weiss
Dr. George Mills
Dr. Rafel "Dwaine" Rieves
Dr. Kathy Robie-Suh
Dr. Andrew Dmytrijuk
Dr. Satish Misra
Dr. Jyoti Zalkikar
Mrs. Diane Leaman

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Diane.Leaman@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to

request an escort to the conference room: Diane Leaman, x (301) 796-1424; the division secretary, x (301) 796-2050.

Provide the background information for this meeting (three copies to the NDA and 13 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by May 12, 2006, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
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 Leaman
4/18/2006 11:03:16 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pharmacia & Upjohn
Attention: Robert B. Clark
Vice President, Pfizer, Inc.
Acting Agent for Pharmacia & Upjohn
235 East 42nd St.
New York, NY 10017

Dear Mr. Clark:

Please refer to your Investigational New Drug Application (IND)/New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to your April 10, 2006 correspondence, received April 11, 2006, requesting a meeting to discuss NDA Supplement-035 and the Agency's action letter dated March 14, 2006.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: May 2, 2006
Time: 1:30 PM – 3:00 PM
Phone Arrangements: CALL-IN NUMBER 1-866-452-4955 AND PASSCODE 828 256 ("Meet-me" Call)
CDER Participants: Dr. Richard Pazdur, Director, Office of Oncology Drug Products (OODP)
Dr. Karen Weiss, Deputy Director, OODP
Dr. George Mills, Director, Division of Medical Imaging and Hematology Products (DMIHP)
Dr. Rafel Rieves, Deputy Director, DMIHP
Dr. Kathy Robie-Suh, Team Leader, Hematology, DMIHP
Dr. Andrew Dmytrijuk, Medical Officer, DMIHP
Mrs. Diane Leaman, Regulatory Project Manager, DMIHP
Dr. Michael Welch, Team Leader, Office of Biostatistics
Dr. Jyoti Zalkikar, Team Leader, Office of Biostatistics
Dr. Satish Misra, Statistician, Office of Biostatistics

Provide the background information for this meeting (three copies to the NDA and 10 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the

information package are inadequate to justify holding a meeting, or if we do not receive the package by April 21, 2006, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager,
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
4/14/2006 02:03:46 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pfizer Inc.
Attention: Robert B. Clark
Vice President, US Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(i)/505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2006. The purpose of the meeting was to discuss the Agency's concerns regarding the analyses of the CLOT study in support of Supplement-035.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager Division of
Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	March 7, 2006
TIME:	2:00 – 2:30 PM
LOCATION:	White Oak Conference Room
APPLICATION:	NDA 20-287/S-035
DRUG NAME:	Fragmin (dalteparin sodium, injection)
TYPE OF MEETING:	Type A (Clinical Advice)
MEETING CHAIR:	Dr. Rafel (Dwaine) Rieves
MEETING RECORDER:	Mrs. Diane Leaman, RPM

FDA ATTENDEES:

Office of Oncology Drug Products (OODP)

Richard Pazdur, M.D., Director
Karen Weiss, M.D., Deputy Director

Division of Medical Imaging and Hematology Products (DMIHP)

George Mills, M.D., Director
Rafel (Dwaine) Rieves, M.D., Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Andrew Dmytrijuk, M.D., Medical Officer
Diane Leaman, Regulatory Health Project Manager

Office of Biometrics V

Aloka Chakravarty, Ph.D., Director

Office of Biometrics, Division of Biometrics II

Milton Fan, Ph.D., Statistician

EXTERNAL CONSTITUENT ATTENDEES:

Andrea Kollath, Regulatory Affairs
Bill Spalding, Statistician
Ben Drosman, Regulatory Affairs
Craig Eagle, M.D., Clinical
Clair Wohlhuter, M.D., Clinical
Connie Newman, M.D., Regulatory Affairs Cardiovascular Therapeutic
David Smith, Esq., Legal
Timera Schmidt, Labeling

BACKGROUND:

On March 16, 2004 (received March 17, 2004), Pharmacia and Upjohn submitted NDA 20-287 Supplement S-035 (S-035) for a new indication for Fragmin for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The NDA was issued an approvable action on January 14, 2005. Pharmacia and Upjohn resubmitted the supplement on September 14, 2005 (received September 15, 2005). On January 24, 2006, the DMIHP sent Pharmacia and Upjohn a letter requesting additional information for S-035.

MEETING OBJECTIVES:

To discuss the Agency's concerns regarding the adequacy of the CLOT study analyses to support the safety and efficacy of the efficacy supplement S-035.

DISCUSSION POINTS:

The Agency started the discussion with the following items:

1. We are completing our review of the information submitted to the NDA, including the safety analyses submitted last fall. We are coming away with an unresolved problem—specifically, the imbalance in study drug discontinuations due to death. We appreciate your assisting us with analyses and efforts to try to resolve the problem but the information leaves us with an important unresolved safety item.

2. We are aiming toward explaining our concern within the upcoming action letter.

3. Given the fairly extensive efforts to try to resolve the problem, we are recommending that you begin consideration of another clinical study to support safety and efficacy.

4. We are calling also to invite you to request a meeting to discuss:

    a. The problem and possible solutions, including new clinical studies.

    b. Ways to address our findings of an important unresolved safety issue, especially in light of the ACCP statements on Fragmin usage among cancer patients with venous thromboembolism.

- The re-analyses of the existing data from the CLOT study cannot explain the discrepancy between the treatment arms in regard to patient deaths. The safety signal needs to be addressed.

- The sponsor suggested that they might seek to study a specific patient population at risk. The Agency reminded the sponsor that an imbalance of patient deaths was seen in the overall population. However, the Agency would be open to review the sponsor's proposals.

- The Agency is planning to have a regulatory briefing at the Office of New Drugs level in the near future.

- Pfizer asked the Agency whether the sponsor's proposed trial in non metastatic cancer patients could be extended to cover this concern. The Agency responded that they will discuss that question internally before responding to the sponsor. The Agency noted that this question could be discussed in a meeting.

- The Agency requested the sponsor provide the extent of off-label use of Fragmin for prophylaxis and extended therapeutic use in cancer patients.

- The Agency will send the sponsor an action letter on or before the PDUFA due date of March 15, 2006. The Agency also expressed concern about the off label use of Fragmin in cancer patients. Following the action, the sponsor may request a meeting to discuss further studies or actions they plan to initiate in order to clarify the discrepancy in the deaths in the trial.

DECISIONS (AGREEMENTS) REACHED:

- The Agency will send the sponsor an action letter on or before the PDUFA due date of March 15, 2006.

- Following the action for S-035, the sponsor may request a meeting to discuss further studies or actions they plan to initiate in order to clarify the discrepancy in the deaths in the CLOT trial.

- The sponsor may request a meeting to be held after the March 15, 2006 action letter to discuss their future actions to address the Agency's concerns regarding the safety of Fragmin for extended use in cancer patients.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Pfizer's plan for future studies to address the safety of cancer patients using Fragmin for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE.

ACTION ITEMS:

- Pfizer will provide the Agency with an estimate of the extent of off-label use of Fragmin for prophylaxis and extended therapeutic use in cancer patients.

- DMIHP will provide Pfizer with an action letter for Supplement S-035 on or before the user fee due date of March 15, 2006.

- Pfizer may request a meeting to discuss their future plans to address the Agency's concerns following receipt of the S-035 action letter.

ATTACHMENTS/HANDOUTS:

N/A

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/s/

Diane V Leaman
3/13/2006 03:56:49 PM

Rafel Rieves
3/13/2006 04:02:34 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2006

To: Andrea Kollath_	**From:** Diane Leaman
Company: Pfizer Global Research & Development	Division of Medical Imaging and Hematology Products
Fax number: 212 857-3558	**Fax number:** (301) 796-9849
Phone number: (212) 733-0466	**Phone number:** (301) 796-1424

Subject: NDA 20-287/S-035: FDA comments

Total no. of pages including cover: 3

Comments: Per our promise during today's meeting, find attached a listing of the critical issues discussed in the meeting.

Document to be mailed: ☐ YES ☑ NO

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Attachment

1. We are winding down our review of the information submitted to the NDA, including the safety analyses submitted last fall. We are coming away with an unresolved problem—specifically, the imbalance in study drug discontinuations due to death. We appreciate your assisting us with analyses and efforts to try to resolve the problem but the information leaves us with an important unresolved safety item.

2. We are aiming toward explaining our concern within the upcoming action letter.

3. Given the fairly extensive efforts to try to resolve the problem, we are recommending that you begin consideration of another clinical study to support safety and efficacy.

4. We are calling also to invite you to request a meeting to discuss:

   a. The problem and possible solutions, including new clinical studies.

   b. Ways to address our findings of an important unresolved safety issue, especially in light of the ACCP statements on Fragmin usage among cancer patients with venous thromboembolism.

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/s/

Diane V Leaman
3/7/2006 05:24:41 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pfizer Inc.
Attention: Robert B. Clark
Vice President, US Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to the teleconference between representatives of your firm and the FDA on February 24, 2006. The purpose of the meeting was to discuss the Agency's request for additional clinical information regarding Table 1.5 in the February 17, 2006 submission to Supplement S-035."

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: February 24, 2006

TIME: 10:00 AM-10:30 AM

LOCATION: Conference Room 2327 (White Oak)

APPLICATION: NDA 20-287/S-035; Fragmin® (dalteparin sodium, injection)

INDICATION: Extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer

TYPE OF MEETING: Clinical Advice

MEETING CHAIR: Dr. Rafel Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Medical Imaging and Hematology Products (DMIHP; HFD-160)

Rafel Rieves, M.D., Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Andrew Dmytrijuk, M.D., Medical Officer
Diane Leaman, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pfizer

Andrea Kollath, Regulatory Affairs
Bill Spaulding, Statistician

BACKGROUND:

On March 16, 2004 (received March 17, 2004), Pharmacia and Upjohn submitted NDA 20-287 Supplement S-035 (S-035) for a new indication for Fragmin for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The NDA was issued an approvable action on January 14, 2005. Pharmacia and Upjohn resubmitted the supplement on September 14, 2005 (received September 15, 2005). On January 24, 2006, the DMIHP sent Pharmacia and Upjohn a letter requesting additional information for S-035. An additional request for information was sent to the sponsor on January 30, 2006, by telefacsimile. On February 3, 2006, Pharmacia and Upjohn requested clarification on the fourth item in the January 24, 3006 information request letter. The Division scheduled a teleconference with the sponsor to clarify the needed information. The Division sent the sponsor a telefacsimile on

February 7, 2006, regarding the statistical analyses requested for review for S-035 for discussion at the February 7, 2006, teleconference. Pfizer submitted an amendment to NDA 20-287/S-035 on February 17, 2006 (received February 21, 2006) in response to the DMIHP request for additional information made at the February 7, 2006 teleconference.

MEETING OBJECTIVE:

To request clarification regarding Table 1.5 entitled "Crude death Rates at Each Study Period (ITT Population) submitted February 17, 2006.

DISCUSSION POINTS:

- Pfizer clarified the following:
    - Table 1.5 describes the crude death rate by month in the ITT population. The table shows differences in the amount of time subjects are on study drug for dalteparin and for OAC. It shows a declining number of patients at risk during the study.
    - The table shows the number of subjects who died during this period regardless of whether they are on treatment or not.
    - In column 4, the number of "subject-months" is the cumulative treatment exposure time during the study.
- DMIHP clarified, and the sponsor agreed, that after six months, the cumulative exposure (time on drug) increases because some patients stayed on study drug longer than six months. The amount of time contributed to the observation goes to 12 months, when patients are no longer on treatment.
- The total numbers in Table 1.5 for death do not match the numbers in the study report. Please revise Table 1.5 to correct for errors and clarify column headers.
- DMIHP requests the sponsor run the same program as was done for Table 1.5 for patients on treatment (up to six months) and generate a similar table for the ITT population up to 12 months of follow-up.
- The sponsor consulted the job of creating the Table 1.5. They will request their consultant to create a new table for patients on treatment.

Conclusions:

Pfizer agreed to submit the requested item as soon as possible. Andrea Kollath will contact Diane Leaman regarding the timeline for submission.

Action Items:

- Pfizer will submit a new table for crude death rates for patients on treatment and up to 12 months follow-up duration.

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/s/

Diane V Leaman
2/27/2006 03:12:46 PM

Rafel Rieves
2/27/2006 04:30:30 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pfizer Inc.
Attention: Robert B. Clark
Vice President, US Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to the teleconference between representatives of your firm and the FDA on February 7, 2006. The purpose of the meeting was to discuss the Agency's request for additional clinical information regarding the study "Randomized Comparison of Low Molecular Weight heparin versus Oral warfarin therapy for long term Anticoagulation in cancer patients with Venous thromboembolism" otherwise known as "CLOT."

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: February 7, 2006

TIME: 10:00 AM-11:00 AM

LOCATION: Conference Room 2327 (White Oak)

APPLICATION: NDA 20-287/S-035; Fragmin® (dalteparin sodium, injection)

INDICATION: Extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer

TYPE OF MEETING: Clinical Advice

MEETING CHAIR: Dr. Kathy Robie-Suh

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Medical Imaging and Hematology Products (DMIHP; HFD-160)

Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Andrew Dmytrijuk, M.D., Medical Officer
Diane Leaman, Regulatory Health Project Manager

Office of Biostatistics

Satish Misra, Ph.D., Statistician, Biologics Therapeutics Statistics Staff

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pfizer

Andrea Kollath, Regulatory Affairs
Joe Heisler, Statistician

BACKGROUND:

On March 16, 2004 (received March 17, 2004), Pharmacia and Upjohn submitted NDA 20-287 Supplement S-035 (S-035) for a new indication for Fragmin for extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer. The NDA was issued an approvable action on January 14, 2005. Pharmacia and Upjohn resubmitted the supplement on September 14, 2005 (received September 15, 2005). On January 24, 2006, the Division of Medical Imaging and Hematology Products (Division) sent Pharmacia and Upjohn a

letter requesting additional information for S-035. An additional request for information was sent to the sponsor on January 30, 2006, by telefacsimile. On February 3, 2006, Pharmacia and Upjohn requested clarification on the fourth item in the January 24, 3006 information request letter. The Division scheduled a teleconference with the sponsor to clarify the needed information. The Division sent the sponsor a telefacsimile on February 7, 2006, regarding the statistical analyses requested for review for S-035 for discussion at this teleconference.

MEETING OBJECTIVE:

To discuss the Division's request for additional clinical information regarding the study "Randomized Comparison of Low Molecular Weight Heparin versus Oral Warfarin therapy for Long Term Anticoagulation in Cancer Patients with Venous Thromboembolism" otherwise known as "CLOT."

DISCUSSION POINTS:

Liver Function Information on Long-term Cancer Patients

The Division noted that information on hepatic enzymes and liver function tests for the subpopulation of patients in the CLOT study who had the longest duration of treatment or the highest doses were not presented in the study data in S-035. The Division requests that, where such data are available from the CLOT study, the sponsor should submit these liver function measures and evaluate and submit change in these measures over time during the course of the study.

The Division requested that the sponsor evaluate additional safety data from cancer patients in other DVT studies that are available to compare with the cancer patients in the CLOT study. Cancer patients from the OAC arm in the CLOT study should also be compared to the cancer patients in the treatment arm in the CLOT study with regard to liver function and hepatic enzymes.

Bleeding Analyses

The sponsor feels the Division's request for the bleeding analyses, in the January 24, 2006 letter, is straightforward and they can provide the information in one and one-half weeks (February 17, 2006).

Death Tables

The Division noted that in the CLOT study, there were more deaths in the Fragmin arm than in the comparator arm. If the population were balanced, one would expect that the number of deaths would be comparable. Please explain the discrepancy.

Sponsor Response:
When a VTE event occurred in the study, the patient was taken off the study drug immediately (first event). Therefore, crossover patients were not analyzed. (Patients from the OAC arm taken off study drug, commonly were placed on Fragmin treatment. Patients on the Fragmin treatment arm taken off drug due to a VTE, commonly were moved to a higher dose of Fragmin.) Subsequent deaths were censored at the first event. For patients

who were censored because of an event, the sponsor followed those patients for 30 days after completion of the protocol. The sponsor did not track the treatment of the patients after the protocol was completed.

The sponsor followed the survival endpoint to 12 months.

The Division requested the sponsor submit what happened to the censored patients. Total deaths could be noted in the table with footnotes. The sponsor should submit a table with two columns; one column with Fragmin and the other the number of deaths during the follow-up period. The time period should show 6-months and 12 months of mortality data on the ITT population. The sponsor should provide the Case Report Forms (CRFs) on all patients who died during the study up to 12 months, including the censored patients.

Platelet Information Request

The sponsor felt the request for thrombocytopenia information in the January 30, 2006 telefacsimile was clear. They will provide the information on bleeding and platelet counts and mortality in two weeks.

In addition to the table, the sponsor should provide KM curves.

Conclusions:

The information requests from January 24 and January 3, 2006 were clarified. The sponsor agreed to submit the requested items.

Action Items:

- The sponsor will provide the bleeding analyses by February 17, 2006.
- The sponsor agreed to submit the number of chemotherapy cycles in a table by February 22, 2006.
- The sponsor will submit the requested death information by February 21, 2006.
- The sponsor will submit the information on bleeding and platelet counts and mortality by February 21, 2006.

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/s/

Diane V Leaman
2/15/2006 02:23:15 PM

Kathy Robie-Suh
2/16/2006 04:01:32 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: February 7, 2006

To: Andrea Kollath	**From:** Diane Leaman
Company: Pharmacia & Upjohn	Division of Medical Imaging and Hematology Products
Fax number: (212) 857-3558	**Fax number:** 301 796-9849
Phone number: (212) 733-0466	**Phone number:** (301) 796-1424

Subject: Clarification of information request for a summary and analysis by treatment, duration and dose of dalteparin sodium from the dalteparin sodium safety database.

Total no. of pages including cover: 5

Comments: For teleconference dated February 7, 2006

Document to be mailed: ☐ YES ☑ NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7510. Thank you.

Attachment

Please provide the following analyses. Please respond with the results by Thursday, February 9, 2006.

1. Please provide analyses that assess the comparison of the composite outcome (venous thromboembolic events or death) between the two study groups:

-through the first four weeks of the study
-through the six month follow-up period
-through the 12 month follow-up period.

2. Please complete the following table where the number of deaths during a specific study week are displayed:

Table 1. Death by Week

Study week	Number of deaths during the study week	
	Fragmin, n =	OAC, n =
1		
2		
3		
4		
5		
6		

3. Please provide a mortality curve that shows the cumulative mortality by study week for each study group (death on y axis, week on x axis). Please develop separate curves for: cumulative through the first six week period; cumulative through the six month study period; cumulative through the 12 month follow-up period.

4. Please develop a graphical display that shows the time of onset of severe thrombocytopenia (platelet count less than 50,000/mcL) by week for the entire six month study period.

Thrombocytopenia tables: Please complete the following tables showing the number and proportion of patients with thrombocytopenia over the course of the study.

	Number of patients/total number of patients (%)	
	Fragmin alone arm	Fragmin followed by OAC arm
Platelet Count <100,000/μl and ≥ 50,000 at 0-6 months	x	x
<1 month	x	x
≥1 month to <6 months	x	x
6 months to 12 months	x	x

	Number of patients/total number of patients (%)	
	Fragmin alone arm	Fragmin followed by OAC arm
Platelet Count ≤ 50,000/μl at 0-6 months	x	x
<1 month	x	x
≥1 month to <6 months	x	x
6 months to 12 months	x	x

5. At your discretion, please provide any additional analyses to address the possibility that the study agent's treatment effect may be impacted by the imbalance in deaths between the two study groups.

6. Please provide transaminase level versus time by any CTC grade and CTC grade ≥ 3 for each of the following: AST, ALT, ALK Phos, GGT, Total Bili, Direct Bili. At the monthly time points starting from month 0 please include the number of patients at that time point. These curves should be generated from the Fragmin safety database. Separate curves should be generated for patients with chronic diseases and acute severe illnesses. Since the CLOT study includes patients that have been most likely ones with the longest duration of exposure to Fragmin, please generate separate curves for this study population.

	Number of patients/total number of patients (%)	
	Fragmin alone arm	Fragmin followed by OAC arm
Number of chemotherapy cycles prior to platelets falling to 50,000-100,000:	X	X
1 cycle	X	X
all	X	X
within 1 week prior to decreasing study drug dose	X	X
2 cycles	X	X
all	X	X
within 1 week prior to decreasing study drug dose	X	X
3 cycles	X	X
all	X	X
within 1 week prior to decreasing study drug dose	X	X
4cycles	X	X
all	X	X
within 1 week prior to decreasing study drug dose	X	X
5 cycles	X	X
all	X	X
within 1 week prior to decreasing study drug dose	X	X
6 cycles	X	X
all	X	X
within 1 week prior to decreasing study drug dose	X	X

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/s/

Diane V Leaman
2/7/2006 01:36:38 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: January 27, 2006

To: Ursula Brown	**From:** Diane Leaman
Company: Pfizer Inc.	Division of Medical Imaging and Hematology Products
Fax number: (212) 672-7866	**Fax number:** (301) 796-9849
Phone number: (212) 733-6354	**Phone number:** (301) 796-1424

Subject: Study 98-FRAG-069 (CLOT study)

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

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Attachment

Please refer to your March 16, 2004 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium, injection).

We also refer to your submission dated September 14, 2005.

We are reviewing the Clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. What was the number of patients that required a dose reduction due to platelet counts greater than or equal to 50,000/microliter but less than 100,000/microliter by treatment group?

2. What was the number of patients that required an interruption in dosing due to platelet counts less than 50,000/microliter by treatment group?

If you have any questions, call me at (301) 796-1424.

Diane Leaman
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products

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/s/

Diane V Leaman
1/30/2006 03:40:16 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

INFORMATION REQUEST LETTER

Pfizer Global Pharmaceuticals
Attention: Robert B. Clark
Vice President, Pfizer, Inc.
235 E. 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your March 16, 2004 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium, injection).

We also refer to your submission dated September 14, 2005.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide the following information for this supplement:

1. A summary and analysis by treatment group for patients with cancer and renal dysfunction of minor and major bleeding for Week 1, Weeks 2 - 4 and Weeks 5 - 35.

2. A summary and analysis by treatment group of both the major and minor bleeding rates that occurred in hematologic cancer patients and clarify the rates for Week 1, Weeks 2 - 4 and Weeks 5- 35.

3. The number of patients with solid tumors who had central venous lines in each treatment group.

4. A summary and analysis by treatment, duration and dose of dalteparin from the dalteparin safety database of evaluations of hepatic transaminases, bilirubin and other measures of liver function. Summarize information on higher doses and longer treatment durations from studies where patients are not chronically ill separately from information from chronically/severely ill patients – as was exactly stated in the approvable letter dated January 14, 2005.

If you have any questions, call Diane Leaman, Regulatory Health Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Kyong Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Kyong Kang
1/24/2006 02:51:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287\S-035

INFORMATION REQUEST LETTER

Pfizer Inc.
Attention: Robert B. Clark
Vice President, US Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your September 14, 2005, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We are reviewing the Clinical section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

You note in your September 14, 2005, correspondence, that you do not plan to (b) (4) Please submit the study protocol for this proposed study.

If you have any questions, call Diane Leaman, Regulatory Health Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Kaye Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Kyong Kang
11/14/2005 09:31:12 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Robert B. Clark
Vice President, Pfizer Inc.
Acting as agent for Pharmacia & Upjohn
235 E 42nd Street
New York, NY 10017

Dear Mr. Clark:

We acknowledge receipt on September 15, 2005, of your September 14, 2005, resubmission to your supplemental new drug application for Fragmin (dalteparin sodium, injection) 2500 IU, 5000 IU, 10,000 IU, 25,000 IU and 7500 IU.

We consider this a complete, class 2 response to our January 14, 2005, action letter. Therefore, the user fee goal date is March 15, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge (b) (4) we will consider deferring the pediatric study during the review of this indication. We will notify you of the details of the deferral upon review of this application.

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Kyong "Kaye" Kang, Pharm.D.,
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V. Moore
11/4/2005 11:05:44 AM
Fo Kyong "Kaye" Kang, Pharm.D.

46 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pharmacia & Upjohn
Attention: Robert B. Clark
Vice President, Pfizer Inc.
Acting as agent for Pharmacia & Upjohn
235 E. 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium, injection).

We also refer to the teleconference between representatives of your firm and the FDA on April 19, 2005. The purpose of the meeting was to discuss the approvable letter for NDA 20-287/S-035 and to clarify the proposed Phase 4 commitments requested by the Division for that supplement.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: April 19, 2005

TIME: 3:00 -4:00 PM

LOCATION: Conference Room 6B-45 (Parklawn)

APPLICATION: NDA 20-287/S-035; Fragmin® (dalteparin sodium) Injection

TYPE OF MEETING: Advice Post Action S-035

MEETING CHAIR: Dr. George Shashaty

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGICDP; HFD-180)

Kathy Robie-Suh, M.D., Ph.D., Acting Deputy Director
George Shashaty, M.D., Acting Hematology Team Leader
Andrew Dmytrijuk, M.D., Medical Officer
Diane Moore, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Jason Zeilonka, M.D., Senior Medical Director, Worldwide Medical, Full Development Team Leader
Jeseph Heissler, Pharm.D., Medical Director, U.S. Medical
Ursula Browne, Senior Manager, US Regulatory Affairs
Diana Hughes, M.D., Medical Director, Risk Management Strategy
Paula C. Abreu, Dr. P.H., Associate Director, Global Biometrics

BACKGROUND:

Pfizer submitted Supplement NDA 20-287/S-035 on March 16, 2004 (received March 17, 2004) for a new indication for the extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)], to prevent recurrent VTE in patients with cancer. DGCDP sent an approvable letter to the sponsor for this supplement on January 14, 2005. On March 25, 2005, Pfizer requested a meeting to discuss the approvable action and the proposed Phase 4 commitments requested by the Division. The background package was sent on April 6, 2005 (received April 7, 2005).

MEETING OBJECTIVE:

To discuss the approvable letter for NDA 20-287/S-035 and to clarify the proposed Phase 4 commitments requested by the Division for S-035.

DISCUSSION POINTS:

In response to the questions in the April 6, 2005, background package, the following agreements were reached after discussion. The format provides the firm's questions in italics followed by DGICDP's responses in bolded lettering.

Question 1.
The sponsor requests participation of clinical staff from the Division of Oncology Drug Products. Does the Division of Gastrointestinal and Coagulation Drug Products Agree?

FDA Response:

For this meeting, your specific request for the Division of Oncology participation was received too late to schedule their attendance.

Question 2.
The sponsor believes that [redacted] (b) (4) *may meet the post-approval commitment to conduct a study of safety and efficacy in patients with cancer who have renal impairment. Does the Division agree?*

FDA Response:

Postmarketing commitments will be agreed upon after review of the resubmission. Patients with serum creatinine greater than 3.6 mg/dL were excluded from the study. This may limit the usefulness of the analysis you propose.

Question 3.
The sponsor believes that a safety and efficacy study in patients with hematologic malignancies and symptomatic VTE as a post approval commitment may not complete within a reasonable time interval and wishes to consider an alternative to meet the post-approval commitment. Does the Division agree?

FDA Response:

No. We are concerned that patients with hematologic malignancies did not appear to fare as well as the other patients in the study. More information on the effectiveness of Fragmin in this population is needed. Postmarketing requirements will be discussed at the completion of the review of the resubmission.

Question 4.
The sponsor believes the subset of subjects with non-metastatic tumors in the clot study is not adequate to statistically support the conclusions the Division has stated. The sponsor believes there is no specific safety or efficacy issue signaled by this study. The sponsor concurs that the number of non-metastatic tumor patients enrolled in clot was small and [redacted] (b) (4) *Does the Division agree?*

FDA Response:

Yes. The Division is willing to consider [redacted] (b) (4) **. You should submit a proposal for your study. The proposed study should have as an additional primary endpoint the** [redacted] (b) (4)

Question 5.
The Division has referred to Canadian registry findings that support the position that use of Fragmin in the pediatric population should be studied. Would the Agency please provide the reference?

FDA Response:

Andrew, M. et al.: Venous Thromboembolic Complications (VTE) in Children: First Analyses of the Canadian Registry of VTE. Blood. 1994; 83(5):1251-1257.

As noted in the above referenced article the incidence for DVT/10,000 hospital admissions can be generally estimated as 5.3. In the study, the authors indicate that out of 137 patients included for analysis 22.6% had cancer. In addition therapy consisted of unfractionated heparin in 115 patients and oral anticoagulation in 103 patients. The authors conclude that, "the frequency of DVT/PE justifies controlled trials of primary prophylaxis in high-risk groups, and therapeutic trials to determine optimal treatment."

Question 6.

(b) (4)

Item 6.
Sponsor believes that "Further studies to investigate how best to transition patients from Fragmin to oral anticoagulation (OAC), should that change in therapy become necessary for a patient" should be undertaken by OAC sponsors or an independent academic group. Does the Agency agree?

FDA Response:

This is an important clinical question that needs to be answered.

Question 7.
The sponsor will provide a safety update for a reporting period commencing October 31, 2003, which represents the cut-off date for data presented in the original clot filing, submitted March 2004. Does the Agency agree with this approach?

FDA Response:

Please provide your proposed cut-off date for the safety update beginning October 31, 2003.

Conclusion:

The sponsor clarified that the cut-off date would be March 15, 2005, for the safety update beginning October 31, 2003. This is acceptable.

Question 8.
Provided all other deficiencies outlined in the "Approvable" letter are compiled and submitted as an amendment, the sponsor would request that the safety update become a post-approval commitment with a specified delivery date subsequent to filing the amendment in place of including it as a component of the pending amendment. Would the Division agree?

FDA Response

No. The Safety Update should be included with your resubmission.

Question 9.
The sponsor would like to schedule a meeting at a future date to gain agreement on the final label. Does the Division agree?

FDA Response:

Yes. After we have received and reviewed your resubmission, we will arrange appropriate labeling discussions with you.

Action Items:

Pfizer will submit the following:

1. A reevaluation of the CLOT data with regard to renal impairment and a detailed description and analysis of the 15 patients who were severely renally-impaired.

2. Reevaluation of the use of Fragmin in patients with hematologic malignancies and proposed language to be included in the package insert to address this patient population.

3. A proposal for a study to determine the efficacy and safety of the use of Fragmin in patients with non-metastatic cancer who develop VTE.

4. A study proposal for pediatric patients with cancer and VTE; consider a multinational approach.

5. In the resubmission, the Safety update will cover the timeframe from October 31, 2003 through March 15, 2005.

6. Material addressing the transition from Fragmin to oral anticoagulant therapy.

7. Further information to address the use of high-dose Fragmin in the first month of treatment compared to the use of oral anticoagulants during the first month of treatment.

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/s/

Diane V. Moore
4/20/05 11:10:15 AM

George Shashaty
4/20/05 11:57:25 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: April 18, 2005

To: Robert B. Clark	**From:** Diane Moore
Company: Pfizer Global Pharmaceuticals	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (212) 672-7866	**Fax number:** (301) 443-9285
Phone number: (212) 573-3412	**Phone number:** (301) 827-7476

Subject: Approvable letter for NDA 20-287/S-035.

Total no. of pages including cover: 5

Comments: **FDA response to questions posed in the April 6, 2005, background package for the meeting scheduled for April 19, 2005.**
The sponsor questions are in italics. The FDA responses are in bold type. You have the option of canceling our meeting scheduled for April 19, 2005, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss or reach agreement on such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible whether you are canceling the meeting.
Sincerely, Diane Moore (301) 827-7476.

Document to be mailed: ☐ YES ☑ NO

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Attachment

Question 1.
The sponsor requests participation of clinical staff from the Division of Oncology Drug Products. Does the Division of Gastrointestinal and Coagulation Drug Products Agree?

FDA Response:

For this meeting, your specific request for the Division of Oncology participation was received too late to schedule their attendance.

Question 2.
The sponsor believes that a (b) (4) *may meet the post-approval commitment to conduct a study of safety and efficacy in patients with cancer who have renal impairment. Does the Division agree?*

FDA Response:

Postmarketing commitments will be agreed upon after a review of the resubmission. Patients with serum creatinine greater than 3.6 mg/dL were excluded from the study. This may limit the usefulness of the analysis you propose.

Question 3.
The sponsor believes that a safety and efficacy study in patients with hematologic malignancies and symptomatic VTE as a post approval commitment may not complete within a reasonable time interval and wishes to consider an alternative to meet the post-approval commitment. Does the Division agree?

FDA Response:

No. We are concerned that patients with hematologic malignancies did not appear to fare as well as the other patients in the study. More information on the effectiveness of Fragmin in this population is needed. Postmarketing requirements will be discussed at the completion of the review of the resubmission.

Question 4.
The sponsor believes the subset of subjects with non-metastatic tumors in the clot study is not adequate to statistically support the conclusions the Division has stated. The sponsor believes there is no specific safety or efficacy issue signaled by this study. The sponsor concurs that the number of non-metastatic tumor patients enrolled in clot was small and (b) (4) *. Does the Division agree?*

Yes. The Division is willing to consider a (b) (4) **You should submit a proposal for your study. The proposed study should have as an additional primary endpoint** (b) (4)

Question 5.
The Division has referred to Canadian registry findings that support the position that use of Fragmin in the pediatric population should be studied. Would the Agency please provide the reference?

FDA Response:

Andrew, M. et al.: Venous Thromboembolic Complications (VTE) in Children: First Analyses of the Canadian Registry of VTE. Blood. 1994; 83(5):1251-1257.

As noted in the above referenced article the incidence for DVT/10,000 hospital admissions can be generally estimated as 5.3. In the study, the authors indicate that of 137 patients included for analysis, 22.6% had cancer. Therapy consisted of unfractionated heparin in 115 patients and oral anticoagulation in 103 patients. The authors conclude that, "the frequency of DVT/PE justifies controlled trials of primary prophylaxis in high-risk groups, and therapeutic trials to determine optimal treatment."

Question 6.

(b) (4)

[redacted]

Item 6.
Sponsor believes that "Further studies to investigate how best to transition patients from Fragmin to oral anticoagulation (OAC), should that change in therapy become necessary for a patient" should be undertaken by OAC sponsors or an independent academic group. Does the Agency agree?

FDA Response:

This is an important clinical question that needs to be answered.

Question 7.
The sponsor will provide a safety update for a reporting period commencing October 31, 2003, which represents the cut-off date for data presented in the original clot filing, submitted March 2004. Does the Agency agree with this approach?

FDA Response:

Please provide your proposed cut-off date for the safety update beginning October 31, 2003.

Question 8.
Provided all other deficiencies outlined in the "Approvable" letter are compiled and submitted as an amendment, the sponsor would request that the safety update become a post-approval commitment with a specified delivery date subsequent to filing the amendment in place of including it as a component of the pending amendment. Would the Division agree?

FDA Response

No. The Safety Update should be included with your resubmission.

Question 9.
The sponsor would like to schedule a meeting at a future date to gain agreement on the final label. Does the Division agree?

FDA Response:

Yes. After we have received and reviewed your resubmission, we will arrange appropriate labeling discussions with you.

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/s/

Diane V. Moore
4/18/05 09:10:33 AM
CSO

George Shashaty
4/18/05 09:56:47 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Pharmacia and Upjohn
Attention: Robert B. Clark
Vice President, Pfizer, Inc.
Acting as agent for Pharmacia & Upjohn
235 E. 42nd St
New York, NY 10017

Dear Mr. Clark:

Please refer to your New Drug Application (NDA 20-287) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to your March 25, 2005, correspondence, received March 25, 2005, requesting a meeting to discuss the post approval study commitments referenced in the January 14, 2005, approvable letter for Supplement S-035.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: April 19, 2005
Time: 3:00 PM – 4:30 PM
Phone Arrangements: A Call-in number and passcode ("Meet-me" Call) will be arranged.
CDER Participants: Drs. Joyce Korvick, Kathy Robie-Suh, George Shashaty, Andrew Dmytrijuk, Stella Grosser and Ms. Diane Moore

Provide the background information for this meeting (three copies to the NDA and seven desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by April 5, 2005, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

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

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/s/

Diane V. Moore
3/29/05 09:27:52 AM

US Medical
Pfizer Inc
235 East 42nd Street 205/10/02
New York, NY 10017
Tel 212 733 6354 Fax 212 309 4462
Email ursula.browne@pfizer.com

Pfizer Global Pharmaceuticals

January 18, 2005

Ursula Browne
Senior Manager
US Regulatory

Joyce Korvick, MD
Director
Food and Drug Administration
Division of Gastrointestinal and Coagulation Drug Products HFD-180
Document Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

RE: FRAGMIN® (dalteparin sodium injection)
NDA 20-287 / Supplement S-035
General Correspondence

Dear Dr. Korvick:

Reference is made to NDA 20-287, Supplement 035, extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer. Reference is also made to facsimile communication from the Division received on Pfizer on January 7, 2005 and associated teleconference held between Pfizer and representatives from DGCDP, held on January 12, 2005, for the purpose of discussing the proposed draft label.

Pfizer hereby retroactively submits for the file, documents provided to the Agency on January 13, 2005 for the purpose of continued deliberation for the proposed product labeling.

The electronic archive copy is contained in a CD ROM approximately 1.56MB in size. The CD ROM has been scanned with McAfee VirusScanTM version 4.5.1 SPI and is virus free.

Please do not hesitate to contact me by telephone (212) 733-6354, or fax (212) 672-7866 as needed.

Respectfully submitted,

Ursula Browne

Ursula Browne

CC: Diane Moore, Project Manager (letter as desk copy)
Division of Gastrointestinal and Coagulation Drug Products HFD-180

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW.

22 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT PHARMACIA & UPJOHN	DATE OF SUBMISSION 01/18/2005
TELEPHONE NO. (*Include Area Code*) 212-573-3412	FACSIMILE (FAX) Number (*Include Area Code*) (212) 672-7866
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 235 E 42nd Street New York, NY 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 20-287

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*) Dalteparin sodium injection	PROPRIETARY NAME (*trade name*) IF ANY Fragmin®
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*) Oligo-Saccharides derived from heparin	CODE NAME (*If any*) Kabi 2165

DOSAGE FORM: Parenteral: Solution for injection	STRENGTHS: **2500 IU, 5000 IU, 10,000 IU, 25,000 IU, 7500 IU**	ROUTE OF ADMINISTRATION: **Subcutaneous**

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
General Correspondence: Response to DRAFT LABEL Proposed by DGCDP, January 13, 2005

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-287

This application contains the following items: (*Check all that apply*)	
	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify) General Correspondence to DRAFT LABEL Proposed by DGCDP, 1/13/05*

CERTIFICATION

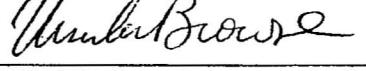
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	ROBERT B. CLARK Vice President, Pfizer Inc. Acting as agent for Pharmacia & Upjohn	01/18/05

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
235 E 42nd Street *New York, NY 10017*	(212) 573-3412

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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FORM FDA 356h (4/00)

US Medical
Pfizer Inc
235 East 42nd Street 205/10/02
New York, NY 10017
Tel 212 733 6354 Fax 212 309 4462
Email ursula.browne@pfizer.com

Pfizer Global Pharmaceuticals

January 18, 2005

Ursula Browne
Senior Manager
US Regulatory

Joyce Korvick, MD
Director
Food and Drug Administration
Division of Gastrointestinal and Coagulation Drug Products HFD-180
Document Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

RE: FRAGMIN® (dalteparin sodium injection)
NDA 20-287 / Supplement S-035
General Correspondence

Dear Dr. Korvick:

Reference is made to NDA 20-287, Supplement 035, extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer. Reference is also made to facsimile communication from the Division received on Pfizer on January 7, 2005 and associated teleconference held between Pfizer and representatives from DGCDP, held on January 12, 2005, for the purpose of discussing the proposed draft label.

Pfizer hereby retroactively submits for the file, documents provided to the Agency on January 13, 2005 for the purpose of continued deliberation for the proposed product labeling.

The electronic archive copy is contained in a CD ROM approximately 1.56MB in size. The CD ROM has been scanned with McAfee VirusScanTM version 4.5.1 SPI and is virus free.

Please do not hesitate to contact me by telephone (212) 733-6354, or fax (212) 672-7866 as needed.

Respectfully submitted,

Ursula Browne

Ursula Browne

CC: Diane Moore, Project Manager (letter as desk copy)
Division of Gastrointestinal and Coagulation Drug Products HFD-180

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW.

23 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Robert B. Clark
Vice President, Pfizer Inc.
Agent for Pharmacia & Upjohn
235 E 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug application dated March 16, 2004, received March 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium, injection) 2500 IU, 5000 IU, 10,000 IU, 25,000 IU and 7500 IU.

We also refer to the meeting between representatives of your firm and the FDA on January 11, 2005. The purpose of the meeting was to discuss outstanding items regarding the review of Supplement S-035.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: January 11, 2005

TIME: 11:30 AM-1:00 PM

LOCATION: Conference Room 17B-43 (Parklawn)

APPLICATION: NDA 20-287/S-035; Fragmin® (dalteparin sodium) Injection

TYPE OF MEETING: Labeling

MEETING CHAIR: Dr. George Shashaty

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGICDP; HFD-180)

Kathy Robie-Suh, M.D., Ph.D., Acting Deputy Director
George Shashaty, M.D., Acting Hematology Team Leader
Andrew Dmytrijuk, M.D., Medical Officer
Diane Moore, Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II (DPEII; HFD-870)

Tien-Mien Chen, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pfizer, Inc.

Ursula Browne, US Regulatory Affairs
Alexandra Pearce, Global Regulatory Leader
Jason Zeilonka, M.D., Full Development Team Leader
Rajesh Aggarwal, Safety and Risk Management

BACKGROUND:

Pfizer submitted Supplement NDA 20-287/S-035 on March 16, 2004 (received March 17, 2004) for a new indication for the extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)], to prevent recurrent VTE in patients with cancer. The original proposed labeling was included in the March 16, 2004, submission. Pfizer amended the labeling on November1, 2004. DGCDP sent Pfizer proposed revised labeling in a telefacsimile on January 7, 2005.

MEETING OBJECTIVE:

To discuss the FDA proposed revised labeling in the January 7, 2005, telefacsimile, the (b) (4) by Pfizer for this supplement.

DISCUSSION POINTS:

1. (b) (4) You must submit a Phase 4 commitment to perform a pediatric study for this indication. For pediatric pharmacokinetic (PK) analysis, a population PK approach is acceptable.

2. The sponsor saw a low incidence of DVT in pediatric cancer patients in the catheter study, but (b) (4).

3. The Division noted that the sponsor can study DVT of the lower extremities, not necessarily patients with catheters only. In the Canadian study that took 10-12 years to perform, the VTE registry included 22% of 115 patients that had cancer and VTE.

4. The sponsor noted that many thromboses occurred as post-radiation thrombosis, not necessarily drug or tumor related.

Additional Phase 4 studies

- There is no documentation of a difference in safety and efficacy in cancer patients with VTE with renal dysfunction based on creatinine clearance.

- The sponsor has proposals from investigators that could present additional data. A study being performed in Canada in critical care patients has about 20% of the patients in the study with cancer with pharmacokinetic/pharmacodynamic (PK/PD) data available in these patients. The sponsor is willing to discuss this type of study as a Phase 4 commitment. The Canadian study (DIRECT) uses a calculated creatinine clearance, but it includes creatinine clearance data.

- The concept presented in the study of reducing or discontinuing the dose of Fragmin in patients with thrombocytopenia appears to be logical, however, there is no data from the study that indicates that changing the dose based on platelet count in patients with VTE and cancer is safe or efficacious.

You should perform safety and efficacy studies in the following patient categories:

1. Cancer patients with renal dysfunction who develop thromboembolism. The dysfunction should be based on creatinine clearance. A creatinine clearance (CLcr) of <30mL/min is considered severe, 30-50mL/min is moderately impaired, 50-80mL/min is mildly impaired and CLcr of >80mL/min is normal (see Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling").

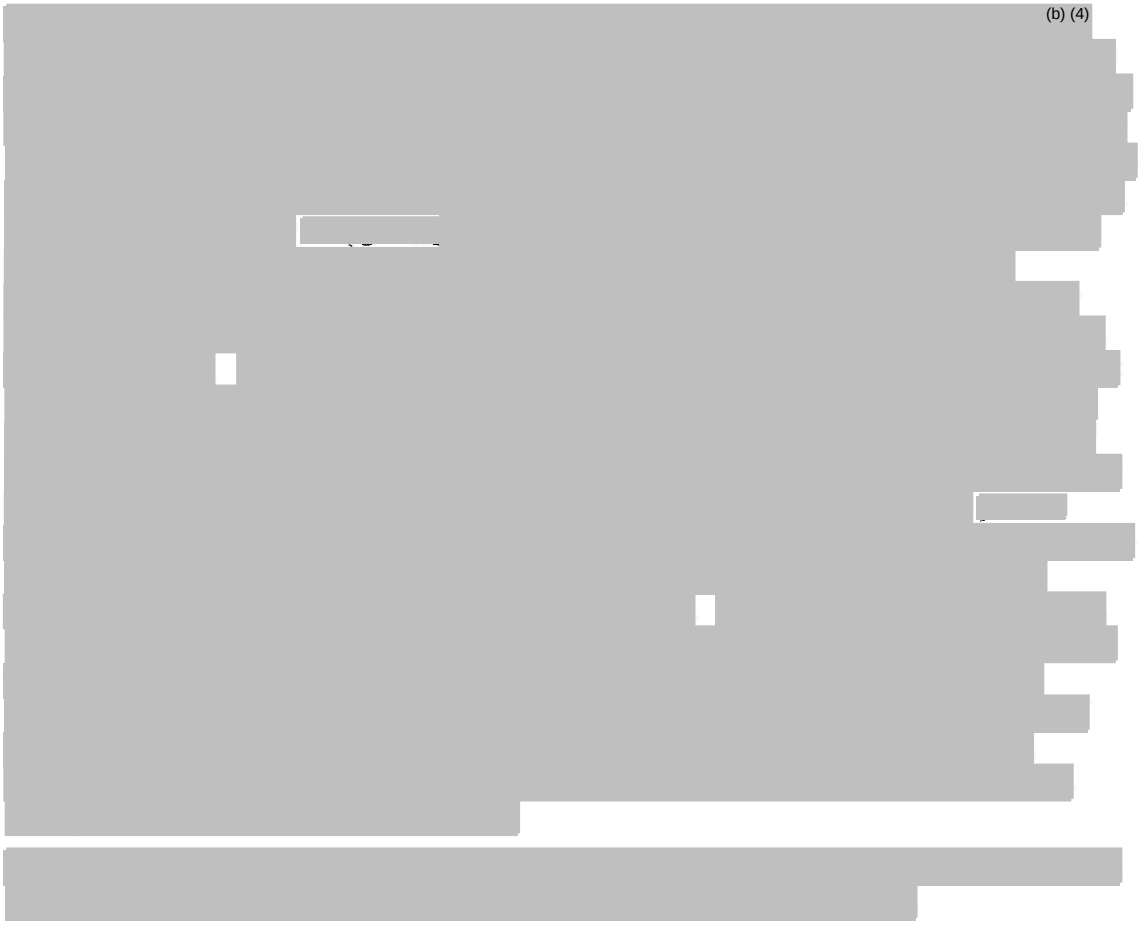
2. Patients with Hematologic malignancies showed a poorer outcome on dalteparin. The sponsor intends to follow-up with additional studies. The study should investigate the safety and efficacy of Fragmin and oral anticoagulant(s) in cancer patients with VTE.

3. Patients with non metastatic tumors seemed to have a higher rate of recurrence while on dalteparin. There may be a difference in tumor burden that may need to be explored.

Labeling

The sponsor agreed with the bulk of the FDA labeling proposals from the January 7, 2005, telefacsimile. The following items were discussed:

1. In the **CLINICAL TRIALS section, Patients with cancer and Acute Symptomatic Venous Thromboembolism** subsection, the first sentence was revised to add the wording that is double-underlined below:



The sponsor objected to the proposed Table 7 entitled "Timing of First VTE (Intention to treat population)[1]". The sponsor felt the deleted Figure 1 gave more information than the proposed table. The sponsor set a 6-month outcome as the primary endpoint of the study and suggested that prescribing doctors might misinterpret the data from Table 7 for dosing. The Division clarified that the peculiarity of the results from the protocol design was not known

until the data was evaluated. The oral anticoagulant (OAC) patients were switched from FRAGMIN to OAC in the protocol, whereas, the FRAGMIN patients received FRAGMIN during the entire study period. The major difference in the two arms occurred in the first month of use. The sponsor noted that the OAC treatment arm was designed to mimic the current state of the art of treatment. Most centers start therapy on low molecular weight heparins (LMWH), give the initial OAC dose and discontinue the LMWH within 48 hours of the INR being in the therapeutic range. The FRAGMIN regimen was new. The Division noted that because cancer patients are in a prothrombotic state, a balance needs to be met between the risk of bleeding (use of higher doses of LMWH) versus the higher rate of VTE in the prothrombotic state. The sponsor noted the regimen used in the OAC arm is approved in other parts of the world. Coumarin does not manifest the full effect until 10 weeks of therapy. The sponsor can propose text to explain the study differences in this section

The Division noted the figure makes it look like FRAGMIN is continuously better than OAC, when after the first 28 days, the lines are parallel. The weekly breakdown of the data is helpful.

Pfizer will send a written proposal for further discussion and verify the data used to create Table 7.

2. **INDICATIONS AND USAGE** section

In the third paragraph, first sentence that begins, "FRAGMIN is also indicated . . . ", the sponsor proposes the phrase [redacted] (b) (4) be replaced by "recurrence of" so that the sentence reads "FRAGMIN is also indicated for the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer." The Division agrees.

3. **CONTRAINDICATIONS** section

The sponsor proposes in the first paragraph, second sentence that begins "Patients undergoing regional . . ." the phrase "for treatment of patients with VTE in patients with cancer" will be added after the term "FRAGMIN" so that the sentence reads "Patients undergoing regional anesthesia should not receive FRAGMIN for [redacted] (b) (4) The Division agrees.

4. **WARNINGS** section, **Thrombocytopenia** subsection

The sponsor will propose wording to modify the first sentence of this section to add cancer patient information. These patients were treated longer than other study subjects.

5. **WARNINGS** section, Drug/Laboratory **Test Interactions** subsection

The sponsor will propose wording to update the numbers in this section.

6. **ADVERSE REACTIONS** section

The sponsor requests that paragraph 12 that begins "A total of 46 (13.6%) of patients in the FRAGMIN . . ." be moved to precede paragraph 11 that begins "Table 12 summarizes major bleeding that occurred . . ."

The Division agrees to the revision.

8. **ADVERSE REACTIONS** section, ***Ongoing safety Surveillance*** subsection

   The sponsor agrees to update this section.

9. **ADVERSE REACTIONS** section, TABLE 12 entitled "Timing of Major Bleeding Events (As treated population)[2]

   The sponsor would like a different data format for Table 12 to display when events occurred because of the nature of the comparison. Pfizer will provide information regarding the weekly breakdown of events similar to the VTE information in Table 7 to validate data in patients with multiple events.

10. The Division proposes the deletion of Table 15 entitled [redacted] (b) (4) Pfizer will provide information regarding the change in thrombocytopenia in patients with renal insufficiency.

Conclusions:

Pfizer will submit the following:

1 A Phase 4 commitment to perform a pediatric study for this indication. You can use population PK approach for pediatric PK data analysis.

2. A Phase 4 commitment to perform a safety and efficacy study on cancer patients with VTE with renal dysfunction based on creatinine clearance who develop thromboembolism.

3. A Phase 4 commitment to perform a safety and efficacy study with Fragmin and an oral anticoagulant on patients with Hematologic malignancies with VTE.

4. A Phase 4 commitment to perform a safety and efficacy study with Fragmin in patients with non metastatic tumors with VTE.

5. Pfizer will submit revised labeling according to the **CLINICAL TRIALS, INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS** and **ADVERSE REACTIONS** sections above.

6. Pfizer will propose text for the **CLINICAL TRIALS** section regarding Table 7 and **ADVERSE REACTIONS** section Table 12.

Action Items:

1. Pfizer will submit a letter to commit to the four Phase 4 studies proposed above.
2. Pfizer will submit revised labeling to NDA 20-287/S-035.

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
1/14/05 05:01:14 PM

George Shashaty
1/14/05 05:03:54 PM

M E M O R A N D U M

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

Date: January 14, 2005

From: Kathy M. Robie-Suh, M.D., Ph.D.
Acting Deputy Director
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Subject: NDA 20-287/SE1-035; submitted 3/16/04
Fragmin (dalteparin sodium) Injection

Efficacy supplement to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer

To: NDA 20-287

Fragmin is a low molecular weight heparin (LMWH) approved (initial approval 12/22/94) for prophylaxis of deep venous thrombosis (DVT), which may lead to pulmonary embolus (PE) in: hip replacement surgery patients, abdominal surgery patients who are at risk for thromboembolic complications, and medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness. Fragmin is also approved for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction (MI), when concurrently administered with aspirin.

In the current supplemental application the sponsor has submitted one multicenter, randomized, open-label, parallel groups, active control, superiority design study (Study 98-FRAG-069; CLOT Study) in cancer patients with an acute episode of objectively confirmed proximal lower limb DVT, PE or both to support the indication of "extended treatment of symptomatic venous thromboembolism (VTE)(proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer." The study enrolled 676 consenting patients (intention-to-treat population) who were randomized equally to the following treatment arms:

- Fragmin arm: dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for one month followed by dalteparin, approximately 150 IU/kg (maximum 18,000 IU s.c. once daily for 5 additional months (total 6 months), or
- OAC arm: dalteparin 200 IU/kg (maximum 18,000 IU) s.c. once daily for 5-7 days while receiving concomitant oral vitamin K antagonist (OAC, usually warfarin) therapy until the INR reached 2-3, at which time the dalteparin was discontinued and

oral anticoagulation was continued for the remainder of 6 months with a target INR of 2-3.

The OAC arm treatment regimen was chosen based on its being a current standard of care. Subjects enrolled in the study were patients age >16 years with active malignancy who are diagnosed with acute, symptomatic proximal lower limb DVT, PE or both, objectively confirmed. Important exclusion criteria were conditions conferring increased risk for bleeding, poor performance status (ECOG status of 3-4), body weight ≤40 kg, significant renal failure, platelet count $<75 \times 10^9$/L, pregnancy or inadequate contraception. The study was designed to demonstrate superiority of the Fragmin arm treatment regimen over the OAC arm treatment regimen for the primary efficacy endpoint of recurrence of symptomatic VTE of the leg(s) or lung during the 6-month study period.

Of the enrolled patients, about 90% of patients had solid tumors (most commonly breast, gastrointestinal or lung). About 10% of patients had hematologic cancers. Baseline characteristics were reasonably well balanced between the two treatment arms. FDA Statistics review (Milton Fan, Ph.D., 12/2/04) found that the Fragmin arm regimen was superior to the OAC arm regimen in reducing the risk of recurrent symptomatic VTE. Time-to-first-event analyses were described using the Kaplan-Meier method for each treatment group and were compared using the log rank test. The Statistical Review states: "A total of 27 of 338 patients randomized to dalteparin (8.0%) and 53 of 338 patients randomized to OAC (15.7%) experienced at least one adjudicated, symptomatic DVT and/or PE during the 6-month study period. The primary comparison of the cumulative probablity of first VTE recurrence over the 6-month study period was statistically significant (2-sided log-rank test, p=0.0017). There was a significant reduction of 52% in the risk of VTE recurrence over 6 months in the dalteparin as the risk ratio of dalteparin to OAC was 0.48 (95% CI, 0.30-0.77, likelihood ratio test, p=0.0016)." The lower recurrent VTE rate in the Fragmin arm was due mainly to a marked reduction in DVT (4.1% in the Fragmin arm as compared to 10.9% in the OAC arm) while the difference with regard to PE was much more modest (3.8% in the Fragmin arm as compared to 4.7% in the OAC arm). Results were similar for the as treated population. There was some inconsistency in results across countries, solid versus hematological tumor, extent of tumor and previous VTE. No difference was demonstrated with regard to survival. The evidence for efficacy provided by the CLOT study alone was found to be not statistically persuasive.

Most of the difference in incidence of VTE events between treatment arms was seen during the second through fourth weeks of study treatment. For weeks 2-4 rates of recurrent VTE were 1.8% in the Fragmin arm and 7.6% in the OAC arm. The Medical Officer's Review (Andrew Dmytrijuk, M.D., 01/14/05) proposes that the level of anticoagulation in the OAC arm during the period immediately following the 5-7 days of dalteparin in the OAC arm may have been inadequate treatment for the heightened thrombogenicity of the early period after development of VTE in patients with cancer and

therefore biased the study in favor of the Fragmin arm where high dose dalteparin (200 IU/kg) was continued for a full month.

The dose of dalteparin proposed for the indication being sought is higher than the doses currently in the Fragmin label (which at this time includes only prophylactic indications). Also, the duration of dosing proposed (6 months) is longer than the labeled duration of dosing for any of the LMWH drugs. The higher dalteparin dose for the treatment indication is understandable considering the well-understood need for greater anticoagulant effect during the acute phase of treatment of an existing VTE. In the CLOT study the extended treatment duration is adequately supported as providing a continued therapeutic benefit in these patients. However, the existing clinical safety database contains limited information on the safety of dalteparin at these higher doses and for 6 months or longer duration.

The Medical Officer's Review (Andrew Dmytrijuk, M.D., 1/14/05) indicates that the safety profile of dalteparin in this study was comparable to the control arm in the overall frequency of adverse events, treatment discontinuations for drug-related adverse events, and frequency of serious adverse events. However, the patients in this study were ill with cancer and, not unexpectedly, there were a large number of deaths (55% of patients in the Fragmin arm and 58% of patients in the OAC arm) and adverse events during the 6-months study duration. Therefore, the ability to discern differences in adverse event profiles between the two treatments in the study was limited. During the 6 months on study, more patients had major bleeding in the Fragmin arm (6.0%) as compared to the OAC arm (4.0%); however, more patients in the OAC arm had any bleeding (18.5%) as compared to the Fragmin arm (13.6%). The Medical Officer's review states that the rate of bleeding was slightly higher in the dalteparin arm (3.8%) compared to the OAC arm (1.5%) in the first 4 weeks of the study. Treatment emergent Grade 3-4 elevation of LFTs (chiefly gamma-glutamyl transpeptidase (GGT) in this study) during the study was seen in 18.3% of patients in the Fragmin arm and 16.9% of patients in the OAC arm. Most of these patients in both treatment arms continued and completed study treatment and outcomes were similar to those seen in the overall population. Elevation of hepatic transaminases has been seen in other studies of heparin and LMWHs.

Other Information:
Other Clinical: Division of Scientific Investigation (DSI) inspected one site (Michael Kovacs, M.D., London Health Science Center; London, Ontario, Canada) for this study. Two minor good faith violations were found and the site was found to be well-onducted and supervised (Khairy W. Malek, M.D., Ph.D., 12/9/04).

The sponsor has submitted (letter date 3/25/04) [redacted] (b) (4) The request has been reviewed and recommendation

made for denial (b) (4). (See Medical Officer's review, Andrew Dmytrijuk, M.D., 01/14/05).

Chemistry, Manufacturing and Controls (CMC): This supplement also provides for registration of four new syringe presentations consisting of 10000 IU (anti-Factor Xa)/0.4 ml, 12500 IU (anti-Factor Xa)/0.5 ml, 15000 IU (anti-Factor Xa)/0.6 ml, and 18000 IU (anti-Factor Xa)/0.72 ml single dose syringe. The CMC information to support the new presentations was found to be adequate (Chemistry review, Ali Al-Hakim, Ph.D., 12/2/04). Microbiology review found the sponsor's decision to withdraw a proposal to use (b) (4) according to validated and approved processes at the Vetter Pharmaa-Fertigung manufacturing facility acceptable (Stephen Langille, 1/4/05). Establishment Evaluation Request (EER) report was found to be acceptable (11/5/04).

Preclinical Pharmacology and Toxicology: There was no preclinical pharmacology and toxicology information in this submission.

Clinical Pharmacology and Biopharmaceutics:
No new human pharmacokinetic (PK) data were submitted and no revisions to the human PK section of the labeling were proposed by the sponsor. The supplement was found acceptable from Office of Clinical Pharmacology and Biopharmaceutics perspective (Tien-Mien Chen, Ph.D., 11/29/04).

Conclusions and Recommendations:
In conclusion, the CLOT study has demonstrated a benefit and acceptable safety of dalteparin 200 IU/kg s.c. daily given for 1 month followed by dalteparin 150 IU/kg s.c. given daily for 5 additional months in extended treatment of acute DVT and/or PE in patients with cancer to reduce the recurrence of VTE in these patients. The benefit of the treatment was most clearly seen during the first month of treatment when for most of the time patients in the OAC arm were just reaching and being stabilized on their OAC dose while patients in the Fragmin arm were receiving high dose dalteparin. The available data do not permit evaluation of the adequacy of anticoagulation during the time when patients in the OAC arm were being transitioned from dalteparin + OAC to OAC alone. Therefore, superiority of the Fragmin regimen over adequate OAC for the indication has not been clearly established. Nevertheless, the Fragmin arm regimen used in this study appears to provide a meaningful clinical benefit with an acceptable safety profile in this indication. The major safety concern for Fragmin in this population is bleeding. As stated in the Secondary Clinical Review (George Shashaty, M.D., 1/14/05), "The current trial is the only available study of dalteparin that provides data for the indication in the population described, but there are a number of studies that indicate its efficacy and safety in the prevention of VTE in other populations." Therefore, Fragmin in the proposed regimen should be made available as a therapeutic option for cancer patients with acute symptomatic VTE and appropriate information to direct its use should be included in the labeling. With regard to the CLOT study, the labeling should reflect that:

- The major benefit of the Fragmin regimen appeared during the first month of treatment.
- Patients with hematologic malignancies in the Fragmin arm tended to have more recurrent VTE events as compared to these patients in the OAC arm. However, these patients represented only about 11% of randomized patients and numbers of events were small.
- There was a higher rate of bleeding during the first month with Fragmin as compared to OAC arm.
- There was no difference in mortality between the two treatment arms of the study.
- Patients with significant renal failure were excluded from the study. There is inadequate information to support the dosing adjustment proposed in the sponsor's labeling for these patients.
- The information available in the submission is inadequate to recommend specific dosing reduction in patients who develop thrombocytopenia on Fragmin; therefore, the table included by the sponsor in the Dosage and Administration section titled [redacted] (b) (4)" should not be included in the labeling.

In the **Clinical Trials** section of the labeling care should be taken to clearly describe the treatment regimens being compared in the CLOT study. In addition, numbers and descriptions of patients studied and findings should be updated in the following sections of the labeling: **WARNINGS, Thrombocytopenia**; **Precautions, Drug/Larboratory Test Interactions:** ***Elevations of Serum Transaminases***; **Precautions, Geriatric Use**; **Adverse Events, Other:** ***Ongoing Safety Surveillance.***

The sponsor should provide summary and analysis by treatment duration and Fragmin dose of data from the Fragmin safety database, including evaluations of hepatic transaminases, bilirubin and other measures of liver function to assess safety of dalteparin at the doses and for the duration proposed for the indication being sought. To more accurately assess possible risk, information on higher doses and longer treatment durations from studies where patients are not chronically ill should be summarized separately from information from chronically or severely ill patients.

Commitment should be obtained from the sponsor to conduct the following post-marketing studies as described in the Medical Team Leader's secondary review (George Shashaty, M.D., 01/14/05). These commitments include:

1. The sponsor should design and conduct a study to further evaluate the effectiveness and safety of Fragmin for treatment and reduction of recurrence of VTE in patients with hematologic cancers.

2. The sponsor should design and conduct a study to further evaluate the effectiveness and safety of Fragmin for treatment and reduction of recurrence of VTE in patients with non-metastatic cancers.

3. The sponsor should design and conduct a study to evaluate the effectiveness and safety of Fragmin for treatment and reduction of recurrence of VTE in patients with cancer and having varying degrees of renal impairment.

4. The sponsor should propose and carry out a plan to address use of Fragmin for the extended treatment of symptomatic VTE in pediatric patients with cancer.

In addition, the sponsor should consider further studies to investigate how best to transition patients from Fragmin to oral anticoagulation, should that change in therapy become necessary for a patient. The CLOT study data suggest and the sponsor has discussed (fax of 1/13/05) that patients being transitioned to OAC may be inadequately protected against recurrent thrombosis, due to pharmacodynamic issues related to time course of depletion of Vitamin K dependent coagulation factors and Proteins C and S.

Additional comments and recommendations from the Medical Officer's Review (Andrew Dmytirjuk, M.D., 1/14/05) and the secondary medical review (George Shashaty, M.D., 01/14/05) should be considered.

cc:
NDA 20-287
HFD-180/DMoore
HFD-180/GShashaty
HFD-180/KRobie-Suh
HFD-720/Sgrosser
HFD-720/MFan
HFD-180/JChoudary
HFD-180/LZhou
HFD-180/AAl-Hakim

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/s/

Kathy Robie-Suh
1/14/05 05:35:54 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

Robert B. Clark
Vice President, Pfizer Inc.
Agent for Pharmacia & Upjohn
235 E 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug application dated March 16, 2004, received March 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium, injection) 2500 IU, 5000 IU, 10,000 IU, 25,000 IU and 7500 IU.

We also refer to the meeting between representatives of your firm and the FDA on January 14, 2005. The purpose of the meeting was to discuss outstanding items regarding the review of Supplement S-035.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: January 14, 2005

TIME: 2:00 -2:30 PM

LOCATION: Conference Room 6B-45 (Parklawn)

APPLICATION: NDA 20-287/S-035; Fragmin® (dalteparin sodium) Injection

TYPE OF MEETING: Clinical Advice

MEETING CHAIR: Dr. George Shashaty

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGICDP; HFD-180)

Kathy Robie-Suh, M.D., Ph.D., Acting Deputy Director
George Shashaty, M.D., Acting Hematology Team Leader
Andrew Dmytrijuk, M.D., Medical Officer
Diane Moore, Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II (DPEII; HFD-870)

Tien-Mien Chen, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pfizer, Inc.

Ursula Browne, US Regulatory Affairs
Alexandra Pearce, Global Regulatory Leader
Jason Zeilonka, M.D., Full Development Team Leader
Rajesh Aggarwal, Safety and Risk Management

BACKGROUND:

Pfizer submitted Supplement NDA 20-287/S-035 (S-035) on March 16, 2004 (received March 17, 2004) for a new indication for the extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)], to prevent recurrent VTE in patients with cancer. The original proposed labeling was included in the March 16, 2004, submission. Pfizer amended the labeling on November1, 2004. DGCDP sent Pfizer proposed revised labeling in a telefacsimile on January 7, 2005. Pfizer submitted proposed revised labeling on January 13, 2005.

MEETING OBJECTIVE:

To discuss the outstanding issues regarding S-035.

DISCUSSION POINTS:

The Division feels that [redacted] (b) (4). You must submit a plan to address the pediatric population for this indication.

In the data from the study for extended treatment of symptomatic venous thromboembolism [VTE (proximal DVT and/or PE)], to prevent recurrent VTE in patients with cancer, there were some subpopulations of cancer patients that responded differently from the main body of cancer patients in the study. Patients with Hematologic tumors and non metastatic malignancies did not respond as well to the treatment as other populations of cancer patients. These patients need to be studied further.

Patients with clinically meaningful renal impairment were excluded from the study. The wording proposed in the labeling is not supported by the data presented. A study should be performed that includes cancer patients with renal impairment who develop VTE

You must propose efficacy and safety studies and designs to address the time course of differences in efficacy between the two treatment arms. Most of the benefit from the use of Fragmin occurred in the first month of use. You should submit a proposal to address the transition of patients from Fragmin to oral anticoagulant therapy (OAC).

Fragmin's previous indications are for prophylaxis. The cancer patients in this study received treatment for VTE rather than for prophylaxis. The dose received was greater and the duration treated was longer than in previous studies. You should perform a safety analysis of your database to support the dose and duration of use. Elevations of hepatic transaminases in the serum should be monitored. A more rigorous evaluation of the database should be performed.

CONCLUSIONS:

The Division will be sending Pfizer revised labeling that includes the FDA revised proposed labeling from January 7, 2005 and the labeling agreements made in the January 11, 2005, teleconference. Further discussion will be necessary to come to a labeling agreement for this supplement.

Once Pfizer receives the Division's comments, Pfizer can request a teleconference to further discuss the outstanding items in this supplement.

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/s/

Diane V. Moore
1/14/05 04:47:44 PM

George Shashaty
1/14/05 05:06:41 PM

1/13/05

Question/Section: CLINICAL TRIALS

Response:
Minor typography, spelling & consistency changes made.

Question/Section: CLINICAL TRIALS: Patients with Cancer and Acute Symptomatic Venous Thromboembolism.

FDA Proposed Labeling:
In a multi-center, open-label, clinical trial, 676 patients with cancer and newly diagnosed, objectively confirmed acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were randomized to either FRAGMIN injection for 6 months (200 IU/kg s.c. [maximum 18,000 IU] once daily for 1 month followed by approximately 150 IU/kg s.c. [maximum 18,000 IU] once daily for 5 months) (FRAGMIN arm) or FRAGMIN injection for a minimum of 5 days 200 IU/kg s.c. [maximum 18,000 IU] once daily and simultaneous oral anticoagulation with a Vitamin K antagonist (OAC arm). Oral anticoagulation was maintained for 6 months adjusted for INR 2.0-3.0. Patients ranged in age from 22 to 89 years of age, median age was 64 years; 51.5% of patients were females; 95.3% of patients were Caucasians. Types of tumors were: breast (16%), lung (13.3%), gastrointestinal tract (23.7%), genitor-urinary (21.5%), hematological tumors (10.4%) or other tumors (15.1%). Venous thrombotic events were adjudicated by a blinded central committee. A total of 27 (8.0%) and 53 (15.7%) patients in the FRAGMIN and OAC arms, respectively, experienced at least one episode of a symptomatic DVT and/or PE during the 6-month study period. Most of the difference occurred during the first month of treatment when patients assigned to the FRAGMIN arm continued to receive FRAGMIN 200 IU/kg s.c. once daily, while patients in the OAC arm received warfarin (see Table 7). In the intent-to-treat population, that included all randomized patients, the primary comparison of the cumulative probability of the first VTE recurrence over the 6-month study period was statistically significant (p=0.0017) in favor of the FRAGMIN regimen. The estimated cumulative probability of recurrence at 6 months was 0.172 in the OAC arm and 0.087 in the FRAGMIN arm. Patients with hematologic tumors had a higher rate of VTE in the FRAGMIN arm (10% [4/40]) than in the OAC arm (0% [0/30]).

Table 7

Timing of First VTE (Intention to treat population)[1]

Study Period	FRAGMIN 200 IU/kg (max. 18,000 IU) sc qd x 1 mo, then 150 IU/kg (max. 18,000 IU) s.c. dq x 5 mo			OAC FRAGMIN 200 IU/kg (max 18,000 IU) s.c. qd x 5-7 d and OAC for 6 mo (target INR 2.0-3.0)		
	Number at Risk	**Patients with VTE**	**%**	**Number at Risk**	**Patients with VTE**	**%**
Total during Study	338	27	8.0%	338	53	15.7%
Week 1	338	5	1.5%	338	8	2.4%
Weeks 2-4	331	6	1.8%	327	25	7.6%
Weeks 5-28	307	16	5.2%	284	20	7.0%

[1] Three patients in the FRAGMIN group and 5 patients in the OAC group experienced more than 1 VTE over the 6 month study period.

Response:
The Division proposed, and the sponsor agreed, to change the initial portion of the clinical statement to better define the two treatment arms and the nature of the treatment in each.

As indicated in the teleconference earlier this week, the sponsor strongly believes that the CLOT study results must be taken in their totality and that separating the efficacy results (or the safety results) into two time periods is not warranted. The wording proposed by the Division gives the impression that after a 30-day period of FRAGMIN therapy, patients will enjoy the same efficacy benefit whether they are continued on FRAGMIN or switched to oral anticoagulation. Such a suggestion is not supported by the CLOT data, and may be incorrect, given the known nature of the pharmacodynamics of warfarin. Pharmacologically, warfarin and its derivatives deplete Vitamin-K dependent factors of coagulation, namely Factors II, VII, IX, and X[1]. Of these, Factor VII has the shortest half-life and the greatest impact on the Prothrombin Time (PT) and the derived International Normalized Ratio (INR). However, patients may not be adequately anticoagulated until Factors IX and X are depleted. There can therefore be a considerable lag between the time that the PT or INR first reaches some desired target

"therapeutic" level and the point when an actual anticoagulant benefit is present[2]. This disparity is further accentuated by the fact that Proteins C and S, natural anticoagulants, are also depleted in parallel with Factor VII.

It may be these subtle (and highly patient specific) timing differences in warfarin-based therapeutic regimens that accounted for the difference in outcomes between dalteparin and oral-anticoagulant-treated patients in the first 30 days of the CLOT study. Thus, in CLOT in the first 4 weeks, 11 dalteparin patients and 33 OAC patients sustained recurrent VTE, a difference of 22 events between study groups (Table 28 of the Final Study Report). Some OAC patients may have been inadequately protected against recurrent thrombosis due to the pharmacodynamic issues discussed in the preceding paragraph, whereas the dalteparin patients, treated with an agent with much more reliable pharmacodynamics and pharmacokinetics, had more uniform and superior protection.

Thus, in suggesting that patients may equivalently be treated with oral anticoagulants or FRAGMIN after day 30 could very well replicate this same disparate event rate when oral anticoagulant therapy is started. As patients transition from FRAGMIN to warfarin after day 30, they could incur the same difference in thrombotic risk that was seen in CLOT in the oral anticoagulant arm in the first 30 days. Thus, in CLOT, during weeks 5-7, 8 patients in each of the FRAGMIN arm and OAC arm suffered a recurrent VTE. If this became the time period during which patients are transitioned from FRAGMIN to an oral anticoagulant, the excess number of events seen in the first 30 days (22 additional VTE events in the OAC arm) could potentially now be superimposed, with a result that 30 OAC patients might suffer a recurrent VTE during this time period rather than 8.

Until or unless there is an actual clinical trial demonstrating comparable safety and efficacy of a treatment arm consisting of 30 days of FRAGMIN followed by 5 months of oral anticoagulation when compared to the FRAGMIN regimen used in CLOT, we believe that the Division's proposed wording in the label does not accurately reflect the clinical implications of the CLOT study. Further, by presenting both the efficacy data (Table 7) and the safety data (Table 11) in this fashion, the Division is suggesting that clinicians should consider a dosing regimen other than the one approved for the indication and providing no guidance on the potential implications of the pharmacology and physiology discussed above.

The sponsor would also request that Figure 1, present in the original draft labeling, be re-inserted into the current label. As noted in the teleconference, the sponsor believes the Kaplan-Meier analysis is the pre-specified analysis of the primary endpoint of the CLOT study. Oncologists, who will make up a considerable portion of the clinicians reviewing this indication and prescribing FRAGMIN, are very familiar with a Kaplan-Meier graphic summarizing study results. However, because we understand the Division's concern (although we do not agree with it) that the Kaplan-Meier curve may be

misinterpreted to imply that FRAGMIN has efficacy beyond the initial 30 day treatment period, we would propose adding some language to point out this concern.

Finally, the Sponsor has reviewed the data in Table 7 and corrected some of the table entries.

Sponsor's Revised Labeling:

(b) (4)

[redacted]

Table 7

(b) (4)

[redacted]


(b) (4)

Question/Section: INDICATIONS AND USAGE

FDA Proposed Labeling:
FRAGMIN is also indicated for the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the frequency of recurrent VTE in patients with cancer.

Response:
Minor typography, spelling & consistency changes made.

During the last teleconference, the sponsor proposed, and the Division accepted, the revision indicated below. This is simpler language and focuses on the relationship of the indication to an individual patient.

Sponsor's Revised Labeling:
(b) (4)

Question/Section: WARNINGS

FDA Proposed Labeling:
Thrombocytopenia:

In clinical trials, the percentage of patients with thrombocytopenia with platelet counts of <100,000/mm^3 (xx) and <50,000/mm^3 (xx) occurred in <1% and <1%, respectively. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed. In clinical trials of patients with cancer and acute symptomatic venous thromboembolism treated for 6 months, thrombocytopenia was reported in 11% of patients in the FRAGMIN arm and in 8.2% of patients in the OAC arm (5 days of FRAGMIN plus OAC followed by OAC drug for the remainder of treatment).

Response:
The Sponsor agrees to provide updated figures for the percentage of patients with thrombocytopenia. As noted below (see PRECAUTIONS), the Sponsor believes that patients with cancer should be reported separately from other, non-cancer, populations. This is because patients with cancer have a different risk profile due to the cancer itself; due to potential thrombocytopenia adverse events related to concomitant medications; and then due to the increased dose and treatment period of FRAGMIN. This section does separate these populations and we agree with this approach.

Sponsor's Revised Labeling:
Values to be provided.

Question/Section: PRECAUTIONS

FDA Proposed Labeling:

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.

Response:

Minor typography, spelling & consistency changes made.

The Sponsor agrees to provide updated values for asymptomatic increases in transaminase levels.

However, because the cancer population represents a target population with a very different risk profile, receives a greater dose of FRAGMIN and is dosed for a considerably longer period, resulting in a greater drug exposure, the sponsor proposes that we provide separate summary data for clinical trials involving primarily patients with cancer and clinical trials not involving patients with cancer as the target population. We realize there may be some minor overlaps (e.g., a trial of post-orthopedic surgery thromboprophylaxis may include patients with cancer), but we would propose that no effort be made to attempt to divide such populations unless patients with cancer make up a considerable part of the population.

Sponsor's Revised Labeling:

(b) (4)

(b) (4)

Question/Section: ADVERSE REACTIONS

FDA Proposed Labeling:

Table 11 summarizes major bleeding that occurred in the clinical trial of patients with cancer and acute symptomatic venous thromboembolism. During the second through fourth weeks of treatment, major bleeding was experienced by more patients in the FRAGMIN arm [9/332 (2.7%)] than by patients in the OAC arm [1/34 (0.3%). Only one bleeding event (hemoptysis in a patient in the FRAGMIN arm at Day 71) was fatal.

Table 11

Timing of Major Bleeding Events1 (As treated population)2

Study Period	FRAGMIN			OAC		
	200 IU/kg (max. 18,000 IU) sc qd x 1 mo, then 150 IU/kg (max. 18,000 IU) s.c. qd x 5 mo			Fragmin 200 IU/kg (max 18,000 IU) s.c. qd x 5-7 d and OAC for 6 mo (target INR 2.0-3.0)		
	Number at Risk	Patients with Major Bleeding	%	Number at Risk	Patients with Major Bleeding	%
Total during Study	338	19	5.6%	338	12	3.6%
Week 1	338	4	1.2%	335	4	1.2%
Weeks 2-4	332	9	2.7%	321	1	0.3%
Weeks 5-24	297	9	3.0%	267	8	3.0%

1 A bleeding event was considered major if it: 1) was accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical symptoms; 2) occurred at a critical site (intraocular, spinal/epidural, intracranial, retroperitoneal, or pericardial bleeding); 3) required transfusion of ≥ 2 units of blood products; or 4) led to death.

2 Patients with multiple major bleeding episodes within any time interval were counted only once in that interval. Howver, patients with multiple bleeding episodes that occurred at different time intervals were counted once in each interval in which the event occurred. A total of 22 and 13 major bleeding events occurred in the FRAGMIN and OAC arms, respectively. Three patients in the FRAGMIN arm and one patient in the OAC arm experienced more than one major bleeding event during treatment.

A total of 46 (13.6%) patients in the FRAGMIN arm and 62 (18.5%) patients in the OAC arm experienced any bleeding event. There were no statistically significant differences in the rate of major bleeding events or the rate of any bleeding event between the two treatment groups. In the FRAGMIN arm, the single fatal bleeding event and the four critical-site bleeding events were associated with the anatomic location of the patient's underlying tumor. In the OAC arm, there was no obvious association between the primary tumor location and the critical bleeding site.

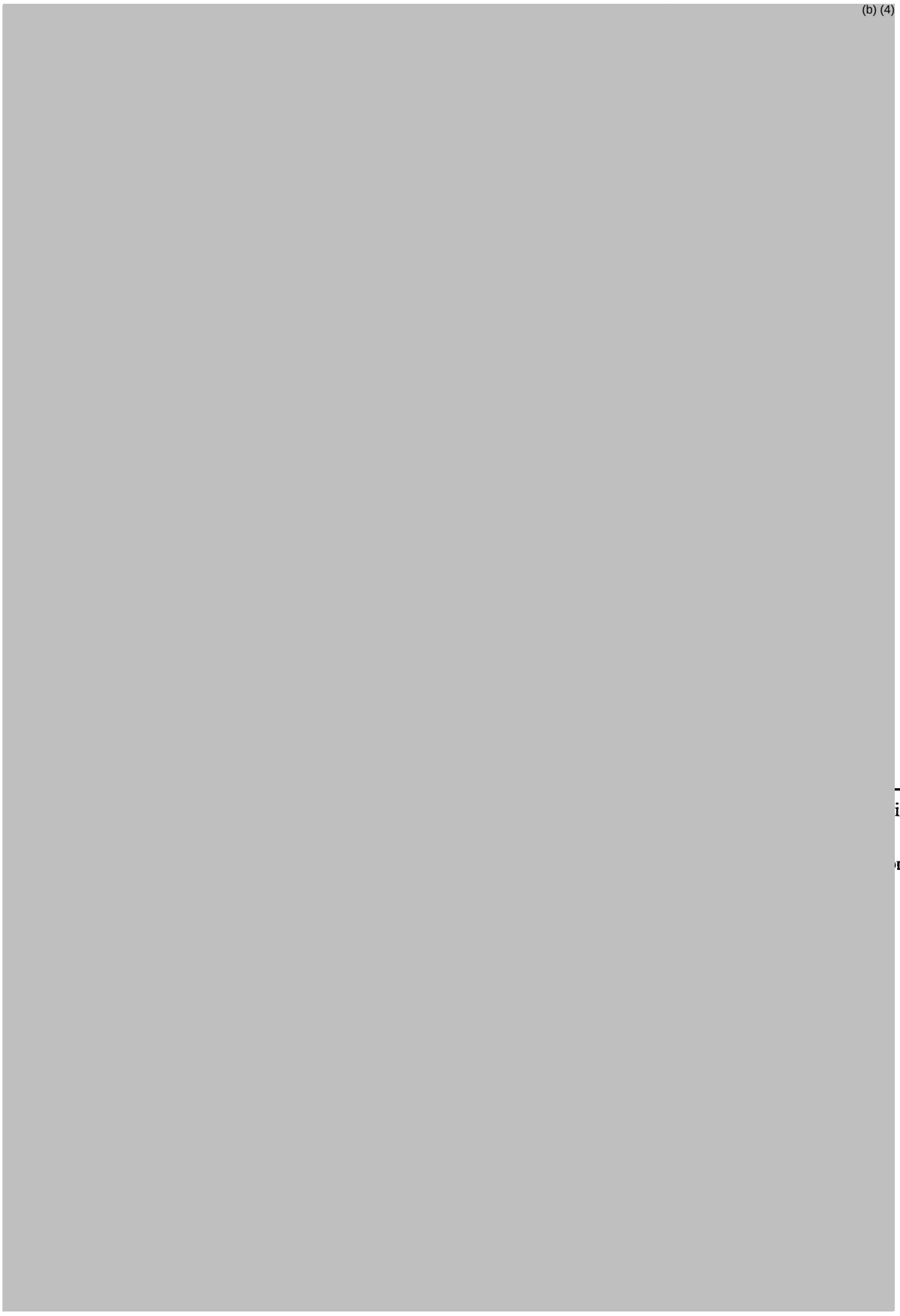
Response:
Minor typography, spelling & consistency changes made, as noted in the FDA Proposed Labeling above.

As noted above (see discussion for Table 7 in CLINICAL TRIALS: Patients with Cancer and Acute Symptomatic Venous Thromboembolism), the sponsor believes that providing data segmented by chronology is not in accordance with the pre-specified primary endpoint of the CLOT study; could lead to incorrect assumptions regarding alternate dosing regimens; and would encourage off-label use through an altered dosing regimen undertaken without any clinical evidence.

Table 11 below provides the safety data in the same chronological display as used in Table 7 for the efficacy data.

Sponsor's Revised Labeling:

(b) (4)


(b) (4)

(b) (4)

Question/Section: DOSAGE AND ADMINISTRATION

FDA Proposed Labeling:

In patients with venous thromboembolism and cancer, the recommended dosing of FRAGMIN is as follows: for the first 30 days of treatment administer FRAGMIN 200 IU/kg total body weight subcutaneously (s.c.) once daily. The total daily dose should not exceed 18,000 IU. Table 14 lists the dose of FRAGMIN to be administered once daily during the first month for a range of patient weights.

Month 1:

Table 14
Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during the First Month

Body Weight (lbs)	**Body Weight (kg)**	**FRAGMIN Dose (IU) (pre-filled syringe)** qd s.c.
< 123.2	< 56	10,000
125.4 to 149.6	57 to 68	12,500
151.8 to 180.4	69 to 82	15,000
182.6 to 215.6	83 to 98	18,000
≥ 123.2	≥ 99	18,000

Months 2 to 6:

Administer FRAGMIN at a dose of approximately 150 IU/kg, s.c. once daily during Months 2 through 6. The total daily dose should not exceed 18,000 IU. Table 15 lists the volume of FRAGMIN to be administered once daily for a range of patient weights during months 2-6.

Table 15
Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during Months 2-6

Body Weight (lbs)	**Body Weight (kg)**	FRAGMIN Dose (IU) (pre-filled syringe) qd s.c.
< 123.2	≤ 56	7,500
125.4 to 149.6	57 to 68	10,000
151.8 to 180.4	69 to 82	12,500
182.6 to 215.6	83 to 98	15,000
≥ 123.2	≥ 99	18,000

Dose reductions for thrombocytopenia in patients with venous thromboembolism and cancer:

Thrombocytopenia: In clinical trials of FRAGMIN in patients with venous thromboembolism and cancer, thrombocytopenia was reported as a treatment-emergent adverse event in 37 (11%) patients in the FRAGMIN arm and 27 (8.2%) patients in the OAC arm.

Twenty-seven out of 338 (8%) patients in the FRAGMIN arm and 5 out of 335 (1.5%) patients in the OAC arm had treatment dose decreases or interruption due to decreased platelet count.

With platelet counts <50,000/mm^3, FRAGMIN should be interrupted until the platelet count recovers above 50,000/mm^3.

Response:
Minor typography, spelling & consistency changes made, as noted above.

We share the Division's concern over the adequacy of the information available to support the dose adjustment for patients with cancer who develop thrombocytopenia while receiving Fragmin. As described in the CSR, section 6.4.5.3. , p. 31 of 7244, the algorithm described in the protocol was empirically developed. The dose reduction was 2,500 IU per day (i.e., reduction to the next lower pre-filled syringe dose) if the platelet count fell between 50,000/mm^3 and 100,000/mm^3. If the platelet count fell below 50,000/ mm^3, dosing was discontinued until the platelet count rose above 50,000/ mm^3. The 50,000/mm^3 and 100,000/mm^3 were selected based on clinical experience with platelet levels that represented clinically significant reduction levels. Other protocols for the development of LMWHs and other anti-thrombotics (oral factor Xa inhibitors, direct thrombin inhibitors) had used the same levels as points at which changes in patient therapy were to be implemented.

We feel it would be valuable for clinicians to be aware that this dose reduction algorithm was used during the CLOT study and that the efficacy and safety results described in this indication were derived with the dosing algorithm described. Accordingly, we would like to include this as historical information relating to the conduct of the clinical trial.

To separate the actual recommendation for dosing from the historical clinical trial information, we have moved the recommendation to the top of the section and made it a separate paragraph.

For the same reason, we would like to include information regarding the dosing algorithm used in the clinical trial in patients who developed renal impairment

during the trial. This would not be actual dosing, but would provide clinicians with additional insight into the clinical trial.

Based on the post-approval commitments we will discuss with you, we would expect that the results of any clinical studies involving patients with cancer and renal impairment would be used to modify this section of the labeling with appropriate information.

Sponsor's Revised Labeling:

(b) (4)

[redacted]

Question/Section: HOW SUPPLIED

FDA Proposed Labeling:
(not included here)

Response:
Sponsor accepted the Division's proposed labeling.

Sponsor Revised Labeling:
No changes proposed.

Question/Section: Is the sponsor willing to agree to the following post-approval commitments?

- A clinical study in patients with cancer and VTE who have renal impairment
- A clinical study in patients with non-metastatic cancer and VTE
- A clinical study in patients with hematological cancer and VTE

Response:
The sponsor agrees in principle with the Division's request and would like to discuss this further with the Division. We are not able to make a firm commitment until we have defined the details of the study design, estimated the cost, and received endorsement from our management.

Question/Section: The Division has considered the sponsor' s (b) (4) **. The Division would like the sponsor to agree to a post-approval commitment to conduct a clinical study in pediatric patients with cancer who develop VTE.**

Response:
The sponsor would like to discuss this further with the Division but is unable to make a firm commitment until we have defined the details of the study design, estimated the cost, and received endorsement from our management.

REFERENCES

1. Goodman LS, G.L., *Goodman & Gilman's pharmacological basis of therapeutics*. 10th ed, ed. L.L. Hardman JG. 2002, New York; London: McGraw-Hill.
2. D'Angelo A, D.P., Crippa L, Fattorini A, Pattarini E, D'Angelo SV, *Relationship between international normalized ratio values, vitamin K-dependent clotting factor levels and in vivo prothrombin activation during the early and steady phases of oral anticoagulant treatment*. Haematologica, 2002. 87(10): p. 1074-1080.

45 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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*** TX REPORT ***
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2005

To: Ursula Brown	**From:** Diane Moore
Company: Pfizer Global Pharmaceuticals	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (212) 672-7866	**Fax number:** (301) 443-9285
Phone number: (212)733-6354	**Phone number:** (301) 827-7476

Subject: Draft revised package insert for NDA 20-287 Supplement S-035.

Total no. of pages including cover: 26

Comments: Please note revisions in the following sections:
DESCRIPTION
CLINICAL TRIALS, Patients with Cancer and Acute Symptomatic Venous Thromboembolism
INDICATIONS AND USAGE
WARNINGS
ADVERSE REACTIONS
DOSAGE AND ADMINISTRATION
Please note: We are concerned that the available information to support the dose adjustment being recommended for cancer patients with thrombocytopenia does not appear to be adequate.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2005

To: Ursula Brown	**From:** Diane Moore
Company: Pfizer Global Pharmaceuticals	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (212) 672-7866	**Fax number:** (301) 443-9285
Phone number: (212)733-6354	**Phone number:** (301) 827-7476

Subject: Draft revised package insert for NDA 20-287 Supplement S-035.

Total no. of pages including cover: 26

Comments: Please note revisions in the following sections:
DESCRIPTION
CLINICAL TRIALS, Patients with Cancer and Acute Symptomatic Venous Thromboembolism
INDICATIONS AND USAGE
WARNINGS
ADVERSE REACTIONS
DOSAGE AND ADMINISTRATION
Please note: We are concerned that the available information to support the dose adjustment being recommended for cancer patients with thrombocytopenia does not appear to be adequate.

Document to be mailed: • YES ☑ NO

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_____ Law Enforcement Action (b7)

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/s/

Diane V. Moore
1/7/05 04:56:42 PM
CSO

From the American Society of Clinical Oncology.
In cooperation with the Food and Drug Administration (FDA), and as a service to our members, ASCO will periodically distribute information about newly approved therapies for cancer patients. This helps FDA to inform oncologists and professionals in oncology-related fields of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. In sending this information, ASCO does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described. The following is a message from the FDA's Office of Oncology Drug Products Director, Dr. Richard Pazdur:

On April 30, 2007 the U.S. Food and Drug Administration granted approval of a new indication for dalteparin sodium injection (Fragmin®, Pfizer, Inc.) to reduce the recurrence of symptomatic venous thromboembolism (VTE) (proximal deep vein thrombosis and/or pulmonary embolism),in patients with cancer. Fragmin is a low molecular weight form of heparin that was initially approved in 1994. With the newly approved indication, Fragmin is the first drug to receive FDA approval specifically for the extended treatment of symptomatic VTE among patients with cancer.

The safety and efficacy of Fragmin were evaluated in an open label clinical study of 676 patients with cancer who had acute deep vein thrombosis and/or pulmonary embolism. Patients were randomized to one of two treatment groups: Fragmin 200 IU/kg daily for one month then 150 IU/kg daily for five months (Fragmin group) or Fragmin 200 IU/kg for five to seven days followed by oral anticoagulation for six months (OAC group). Fragmin was administered subcutaneously and daily dose did not exceed 18,000 IU. The types of underlying cancers included: breast (16%), lung (13%), gastrointestinal tract (24%), genito-urinary (22%), hematological (10%) and other types (15%). Patients were followed for the recurrence of VTE over the entire six month treatment period and VTE events were adjudicated by a central committee masked to treatment assignments.

A total of 27 (8.0%) and 53 (15.7%) patients in the Fragmin and OAC groups, respectively, experienced at least one episode of recurrent VTE ($p = 0.002$). Most of the treatment difference occurred during the first month of the study and this difference was maintained throughout the subsequent five months. Mortality rates were similar between the study groups at the end of the study. The safety findings were most notable for numerically higher rates of the following events among more Fragmin than OAC group patients: major bleeding events (6% vs 4%), thrombocytopenia adverse events (11% vs 8%) and serum ALT and AST enzyme elevations of grade 3 or higher severity (4% vs 2%; 3% vs 1%). These data were discussed at a September 6, 2006 meeting of the Oncologic Drugs Advisory Committee.

The recommended Fragmin dose regimen for patients with cancer and VTE consists of: 200 IU/kg once daily for the first month followed by 150 IU/kg once daily for the subsequent five months. All Fragmin doses are administered subcutaneously and should

not exceed a daily dose of 18,000 IU. No monitoring of blood anticoagulation tests is necessary for this usage.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications, is available at www.....

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_____ Deliberative Process (b5)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 7, 2004

Diane Moore, Regulatory Health Project Manager
Andrew Dmytrijuk, M.D., Clinical Reviewer
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

THROUGH: Ni Khin Aye, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: Khairy W. Malek, M.D., Ph.D., Reviewer

SUBJECT Evaluation of Clinical Inspections

20-287/S-035

APPLICANT: Pfizer Healthcare

DRUG: Fragmin (dalteparin sodium) injection

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Extended treatment of Symptomatic venous thromboembolism (VTE) to prevent recurrent VTE in patients with cancer.

CONSULTATION REQUEST DATE: October 8, 2004

INSPECTION SUMMARY GOAL DATE: December 13, 2004

ACTION GOAL DATE: January 7, 2005

1 BACKGROUND:

Fragmin (dalteparin sodium) is a LMWH (low molecular weight heparin). The study objective is to compare the relative efficacy and safety of the LMWH dalteparin sodium (Fragmin) with those of oral anticoagulant therapy using a coumarin derivative for long term coagulation in cancer patients with acute VTE.

The study is an international, multicenter, open-label, randomized trial, in which cancer patients with acute symptomatic proximal lower limb DVT (deep venous thrombosis) or PE (pulmonary embolism) are randomized to two groups at the time of confirmed VTE (DVT or PE) diagnosis:

1. Experimental arm: patients receive full therapeutic dose of Fragmin (200 I.U./kg once daily, subcutaneously) for a minimum of 5 days and continue to receive Fragmin at the full therapeutic dose for the first month and then receive a reduced dose for the remainder of the 6 month study period.
2. Control arm: patients receive the full therapeutic dose of Fragmin for 5 days and take oral anticoagulant therapy with a coumarin derivative along with Fragmin as the initial therapy. After receiving Fragmin for a minimum of five days and once the INR has achieved the therapeutic target range of 2-3 for two consecutive days, patients of this group continue with oral anticoagulant therapy alone for the remainder of the 6 month study period.

Diagnosis of lower limb DVT must be confirmed by one of the following criteria:

a. Constant intraluminal filling defect in two or more veins on contrast venography in one or more proximal venous segments (iliac, common femoral, superficial femoral, or popliteal vein).
b. New or previously undocumented non-compressibility of one or more proximal venous segments [common femoral or popliteal vein] on CUS (compression ultrasonography).

Diagnosis of PE in a patient suspected PE must be confirmed by meeting one of the following criteria:

a. An intraluminal filling defect on a pulmonary angiogram.
b. Sudden contrast cut-off of one or more vessels more than 2.5 mm in diameter on a pulmonary angiogram.
c A high probability VQ lung scans showing one or more segmental perfusion defects with corresponding normal ventilation.
d. An abnormal but non-high probability VQ lung scan with satisfaction of the criteria for lower limb DVT.

Efficacy Outcome Events:

The primary efficacy outcome event is symptomatic recurrent VTE of the legs or lung during the six-month study period.

2. The secondary efficacy outcome during the six-month study period are:

a. Bleeding (major and all bleedings).
b. New, symptomatic, objectively documented DVT, PE or central venous thrombosis of the upper limb(s), neck or chest.
c. Death

II. RESULTS (by protocol/site)

Study 98-FRAG-069

Site #1 Michael Kovacs, M.D.
London Health Science Centre
London, Ontario, Canada

This was the only site inspected for this study. I reviewed the records of 36 subjects out of 64 enrolled in the study. The assignment was sent 10/12/2004 and the inspection ended on December 3. There were two minor violations found:

1. Subject 106-034: The PI enrolled this subject on suspicion and equivocal ventilation/perfusion lung scan on 8/23/04 (enrollment date). The radiologist report stated that perfusion was decreased compared to ventilation but this was likely caused by previous radiotherapy and considered it a "low probability lung scan". Another VQ lung scan was done after a week and it was negative for PE. The subject was withdrawn from the study on the same day (8/30).
2. Subject #106-20: The PI was informed verbally by the ultrasound department that the patient had a clot into the popliteal vein (DVT) and he randomized the subject. The written report came that it was in a distal vein. The PI contacted Dr. Levine (Chair of the steering committee) he allowed the subject to continue as he had the disease of interest (thombosis and cancer).

These were minor good faith errors and no Form 483 was issued and the classification was NAI. The data from this study can be used in support of the NDA supplement.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Inspection of this site showed that it was well conducted and supervised

No follow up is needed.

Signature
Khairy W. Malek, M.D., Ph.D.

CONCURRENCE

Supervisory comments Concur Joseph P. Saleweski for 12-9-04

Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

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NDA 20-287/S-035
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File name:O:/KM/Fragmin Summary

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/s/

Diane V. Moore
12/15/04 10:12:21 AM
CSO
For Khairy W. Malek, M.D., Ph.D. and Joseph P. Salewski for Chief, Good Clinical Practice Branch I, Division of Scientific Investigations

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: November 23, 2004

From: Shannon Benedetto

To: Diane Moore
Re: Fragmin (dalteparin sodium injection)
NDA 20-287/S-035
Document Date October 27, 2004

General Comment

We note that the proposed indication uses the phrase "to prevent," i.e., to prevent recurrent VTE in patients with cancer. Current CDER recommendations are that we try to avoid the term "prevent" in labeling because it implies absolute efficacy, i.e., 100%. Alternatives could include "reduce the risk of" or "reduce the incidence of." We ask that these changes be made to the wording of the indication. Once the language has been finalized, it would also need to be applied to the many subheadings throughout the label, e.g., in Clinical Studies, Adverse Reactions, Dosage and Administration, etc.

Clinical Studies

1. (b) (4)

Use of the term (b) (4)" is promotional in tone. DDMAC recommends deletion of (b) (4) from the proposed language.

2. (b) (4)
"

We recommend that the relative risk results be deleted (unless it is particularly clinically important) because it could be used promotionally.

INDICATIONS AND USAGE

"FRAGMIN is also indicated for the ***extended treatment*** of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to prevent recurrent VTE in patients with cancer."

According to the clinical study section, patients were treated and followed for 6 months. Should the indication reflect a 6 month treatment period or state that controlled studies do not extend beyond 6 months?

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/s/

Shannon Benedetto
11/23/04 03:30:38 PM

Moore, Diane V

From: ees_admin@bambi.cder.fda.gov
Monday, November 01, 2004 3:09 PM
MOORED@cder.fda.gov
Subject: Delayed EER Initiated NDA 20287/035 CFN: 9610708 Profile: CTL

This is a system generated message to notify you that the above EER has been added to this Application after reaching the OC Recommendation Milestone.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@CDER.FDA.GOV).
To contact the EES technical staff, send an email to CDER EES Help (EESHELP@CDER.FDA.GOV). Thank you.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-287/S-035

Pharmacia & Upjohn Company
Attention: Robert Clark
Vice President, Regulatory Affairs
235 E. 42nd St.
New York, NY 10017

Dear Mr. Clark:

Please refer to your March 16, 2004, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on May 16, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. A single pivotal study, Study 98-FRAG-069, titled "Randomized Comparison of Low-Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism" (CLOT), is submitted for the indication. More than one study is usually required for approval. Please refer to the guidance titled, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)."

2. The dropout rate in the CLOT study is large. About 49% of the patients failed to complete study treatment.

3. In the CLOT study, death, particularly death due to underlying cancer, during treatment appears significantly greater in the dalteparin group as compared to the oral anticoagulant group.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-035

PRIOR APPROVAL SUPPLEMENT

Pharmacia & Upjohn Company
Attention: Robert Clark
Vice President, Regulatory Affairs
235 E. 42nd St.
New York, NY 10017

Dear Mr. Clark:

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)

NDA Number: 20-287

Supplement number: S-035

Review Priority Classification: Standard (S)

Date of supplement: March 16, 2004

Date of receipt: March 17, 2004

This supplemental application proposes the following change: to add a new indication for the extended treatment of symptomatic venous thromboembolism (VTE) [proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)] to prevent recurrent VTE in patients with cancer.

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 May 14, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 17, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt on March 26, 2004, of your March 25, 2004, request (b) (4). Once the application has

been filed we will notify you whether [redacted] (b) (4)

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

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

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/s/

Diane V. Moore
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MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 28, 2003

TIME: 3:00 - 4:30 PM

LOCATION: Chesapeake Conference Room (Parklawn)

APPLICATION: NDA 20-287; Fragmin® (dalteparin sodium) Injection

TYPE OF MEETING: Pre-Supplemental NDA (sNDA)

MEETING CHAIR: Dr. Kathy Robie-Suh

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGCDP; HFD-180)

Robert Justice, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Ruyi He, M.D., Medical Officer
George Shashaty, M.D., Medical Officer
Diane Moore, Regulatory Project Manager
Ryan Barraco, Regulatory Health Project Manager

Division of Biometrics II (DBII; HFD-715)

Mushfiqur Rashid, Ph.D., Biometrics Team Leader

Office of Drug Evaluation III (HFD-003)

Zei-Pao Huang, M.S. Regulatory Health Information Specialist

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pfizer Inc.

Chris Bowden, MD., Clinical Program Director, Global Clinical Research, Oncology
Anna Polli, BC St., Senior Statistical Program Leader, Oncology
(b) (4)
Agnes Lee, MD., Consultant, Coordinating Investigator, Clinical Trials Methodology Group
Gregg Larson, MD., Team Leader/Clinical Director
Jason Zielonka, MD., Full Development Team Leader
Jim Stolzenbach, PhD., Vice President, Product Development
H. Scott Greenberg PhD., Senior Project Manager, Project Management
Allen Crook, Pfizer Global Pharmaceuticals
Alexandra Pearce, Ph.D., Regulatory Liaison Director, World Wide Strategy
Gregory A. Brier, Senior Regulatory Manager, Global Regulatory Affairs

BACKGROUND:

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

On October 13, 1999, (received October 14, 1999) Pharmacia and Upjohn submitted the protocol entitled "Randomized Comparison of Low-Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism" (CLOT) Study (98-FRAG-069). DGCDP provided comments in a February 16, 2000, letter. On December 11, 2002, the sponsor requested a meeting to discuss the sponsor's questions regarding the use of this study to support a proposed indication for Fragmin (dalteparin sodium) Injection for extended prophylaxis of recurrent DVT and/or PE in patients with cancer. The sponsor also is seeking to submit the supplemental NDA (sNDA) in a Common Technical Document (CTD) format. On December 11, 2002, a meeting was held between representatives from Pharmacia and Upjohn and DGCDP. On August 29, 2003, (received September 2, 2003) Pfizer requested a pre-sNDA meeting to discuss the results of the CLOT study and other supporting studies for the indication of treatment of symptomatic Venous Thromboembolism (proximal DVT and/or PE) and for extended prevention of its recurrence in patients with cancer. Pfizer noted on the
August 29, 2003, submission that Pharmacia & Upjohn Company is the sponsor of NDA 20-287 FRAGMIN® (dalteparin sodium injection) and a wholly owned subsidiary of Pharmacia Corporation. Pharmacia Corporation is a wholly owned subsidiary of Pfizer. Pfizer is the authorized agent for this NDA. Pfizer submitted the background package for the meeting on September 26, 2003 (received September 29, 2003).

MEETING OBJECTIVE:

To discuss questions posed by Pfizer in the background package dated September 26, 2003, (received September 29, 2003) submitted to NDA 20-287 regarding a future efficacy supplement for a proposed indication of Fragmin® (dalteparin sodium) injection of treatment of symptomatic Venous Thromboembolism (proximal DVT and/or PE) and for extended prevention of its recurrence in patients with cancer.

DISCUSSION POINTS:

- The Division supplied the sponsor with the responses to the proposed questions on October 21, 2003. In response to the concerns listed, the sponsor presented some information regarding the supporting studies during this meeting (see attached slides).

- The planned submission date for the supplemental NDA is the end of December 2003 or early January, 2004.

QUESTIONS: (background package submitted September 26, 2003, received September 26, 2003)

In response to the firm's questions in their September 26, 2003 submission, the following agreements were reached after discussion. The format provides the firm's questions, followed by the Agency's responses in bolded lettering.

Question 1.: Pfizer considers that, taken together, the results of ten studies sponsored by the Company and additional published literature summarized in the briefing document, adequately address the Division's questions raised during the December 11, 2002, guidance teleconference. These questions were as follows:

a. Whether the choice of control arm for the CLOT study was appropriate.

b. Whether the rationale for establishing the dose/regimen for FRAGMIN used in the CLOT trial was appropriate.

c. Whether the prospectively planned analyses and results of Pfizer's CLOT trial, supported by additional clinical data:
   - Establish the effectiveness of FRAGMIN (as part of an initial regimen combined with OAC) in the acute treatment of VTE (i.e. is a an acceptable standard or care) and,
   - Demonstrate the safety of long-term use of FRAGMIN.

Does the Division agree that the proposed data package, summarized in the briefing document, supports the filing of an sNDA?

FDA Response:

- **The proposed data package appears to be adequate for filing. How well the submitted information addresses the concerns raised is a review issue.**

- **Include follow-up data for both primary and secondary endpoints (6-9 months). The sponsor explained that no data was captured after six months except adverse events and survival data. The sponsor will need to address long-term management of patients beyond six months treatment.**

- **Clarify how many patients have had long-term (>1 month) treatment with Fragmin at the dose being proposed for the new indication. Provide analysis of safety data for this population. The sponsor clarified that 80% of patients in the CLOT study were treated for greater than one month.**

- **Provide efficacy and safety results analyzed by Fragmin treatment dose and duration for all patients.**

- **The acceptance of the single study as a sufficient scientific and regulatory basis for approval of Fragmin for the new indication will be determined by the strength of the results.**

Question 2.: It is proposed the CTD will contain the following data in support of the new indication:

a. Results from Pfizer study reports and other published scientific literature to support the treatment of VTE using FRAGMIN as part of an initial regimen combined with OAC as a standard or care and that the novel regimen used in the experimental arm of the CLOT study is superior to this standard of care.

b. Results from Pfizer study reports and other published scientific literature to support long-term (>1 month) efficacy and safety of FRAGMIN in various patient populations.

c. Safety and efficacy data and results of statistical analyses from the CLOT study in support of the proposed indication.

Are the contents of the proposed CTD acceptable to the Division?

FDA Response:

- **The contents of the proposed CTD appear to be acceptable. However, we have the following comments:**
  - **Please provide all follow-up efficacy and safety results for all patients who received long-term (>1 month) use of Fragmin at different doses.**
  - **Data to support the dose selection will need to be included in the NDA application.**
  - **Primary data should be submitted for all Pfizer studies not previously submitted that are considered to provide meaningful support for the desired indication. The sponsor will supply study reports, data listings and other information from Pfizer studies that they feel are relevant to the desired indication.**
  - **Where available, primary data should be submitted for any non-Pfizer published studies considered to provide meaningful support for the desired indication. The sponsor clarified that they do not have access to primary data from any of the non-Pfizer studies.**

Question 3.: Pfizer regards the recently completed CLOT study as pivotal in supporting the new indication. In addition, ten supportive Company-sponsored studies and other studies published in the scientific literature will be provided in the CTD. The proposed content of the CTD is as follows:

a. Copies of Pfizer study reports and other studies published in scientific literature. Since some of these studies were conducted 10 to 20 years ago, it is proposed to provide only the data analyses included in the study reports and/or published literature.

b. For the pivotal CLOT study, in addition to the complete study report and individual patient profiles, Pfizer will provide the electronic case report tabulations (CRTs) including all data

collected and all calculated variables used in the analyses as SAS transport files along with the SAS program codes for the most relevant statistical analyses of the primary and secondary efficacy and safety endpoints.

c. As requested by the Division during our December 2002 guidance teleconference, in addition to submitting the CTD on CD-ROM, a paper copy of the clinical efficacy sections will be provided for the medical reviewer and a paper copy of the pharmacology section provided for the pharmacology reviewer. Three copies of the summary sections will also be provided.

Does the Division find the CTD contents and submission satisfactory as described?

FDA Response:

- **The CTD contents and submission appear to be adequate, however, we have the following comments:**

  - **Provide patient profiles for the Pfizer studies, not previously submitted, that are considered to provide meaningful support for the desired indication. The sponsor clarified that in the last four studies contained in Table 1 of the briefing package (entitled "Pfizer Sponsored Studies with Dalteparin 1986-1992"), the dose was 200 IU/kg/day (similar to proposed doses for the indication) for a shorter duration. The sponsor will provide patient profiles for those studies.**

  - **Supporting analyses of the efficacy results for the pivotal study (e.g., such as by age, by important risk factors, by geographic area) should be included in the NDA submission.**

  - **Clarify whether this will be an electronic submission as per the guidance or a paper submission in the CTD format with electronic components. The sponsor clarifies that this is a CDT CD ROM with a paper copy**

Question 4.: FRAGMIN has been marketed for approximately nine years in the USA and safety updates have been provided to the Agency on a regular basis. We plan to include both the safety information collected from the CLOT study in support of this indication, a summary of safety information for any patient population that relates to the treatment of acute DVT or PE and all results that relate to long-term (>1 month) therapy in all studies, including literature summaries.

Does the Division agree that this will provide adequate information to demonstrate the safety of FRAGMIN with respect to the proposed indication?

FDA Response:

- **The proposal appears to be adequate. However, we have the following comments:**

  - **For the CLOT study, provide also analysis/presentation of safety results, particularly bleeding events, by time of occurrence.**

  - **Provide analyses of the safety information obtained from studies in cancer patients. The sponsor clarifies that they will provide safety data from the CLOT study and safety data from the 98-FRAG-076 study, individually.**

Question 5.: The Statistical Analysis Plan for the pivotal CLOT study produced before data base lock, a detailed description of the statistical methods used to present data in the study report and key efficacy variable displays are provided in Appendix VII.

Does the Division anticipate any other analysis that would be relevant during the assessment?

FDA Response:

- **Submit subgroup analyses by race, age-group, gender and country.**

(b) (4)

[redacted]

Action Items

- The sponsor will provide primary safety and efficacy data from the Pfizer studies including study reports, data listings, dosing information, follow-up safety data and other relevant information and patient profiles and other available data from non-Pfizer studies in the sNDA submission.
- The sponsor will provide safety data from the CLOT study and safety data from the 98-FRAG-076 study.

{See appended electronic signature page}

Signature, recorder

{See appended electronic signature page}

Signature, Chair

drafted: dm/10/31/03
revised:
initialed: K.Robie-Suh 11.5.03
Finalized: November 6, 2003
Filename: N20287MM102803.doc

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/s/

Diane V. Moore
11/6/03 12:13:00 PM

Kathy Robie-Suh
11/7/03 12:02:30 PM

MEMORANDUM OF TELECONFERENCE

MEETING DATE: December 11, 2002

TIME: 3:00 - 4:30 PM

LOCATION: Conference Room "L" (Parklawn)

APPLICATION: NDA 20-287; Fragmin® (deltaparin sodium) Injection, 5000 IU

INDICATION: Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism (VTE)

TYPE OF MEETING: Guidance (Clinical)

MEETING CHAIR: Dr. Robert L. Justice

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGICDP; HFD-180)

Robert Justice, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader
Ruyi He, M.D., Medical Officer
Edvardas Kaminskas, M.D. - Medical Officer, DGICDP (HFD-180)
Diane Moore, Regulatory Project Manager

Division of New Drug Chemistry II (DNDC II) @ DGICDP (HFD-180)

Liang Zhou, Ph.D., Chemistry Team Leader

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Pharmacia and Upjohn Company

Langdon Miller, M.D., Vice President, Oncology, Global Clinical Research, Oncology
Chris Bowden, M.D., Clinical Program Director, Global Clinical Research, Oncology
Kerry Barker, Ph.D., Director Biostatistics, Global Clinical Research, Oncology
H. Scott Greenberg, Ph.D., Senior Project Manager, Project Management
Jim Stolzenbach, Ph.D., Vice President, Product Development
Sharon Olmstead, Executive Director, FDA Liaison, Global Regulatory Affairs
Christopher Griffett, Executive Director, Global Regulatory Affairs
Gregory A. Brier, Senior Regulatory Manager, Global Regulatory Affairs
Prem Narang, Ph.D., Senior Director, Global Regulatory Affairs
Satish Tripathi, Ph.D., Director, Global Regulatory Affairs

NDA 20-287
Fragmin
Meeting Minutes - December 11, 2002

Clinical Trials Methodology Group (Consultants)

(b) (4)

Agnes Lee, M.D., Consultant, Coordinating Investigator

BACKGROUND:

Fragmin was approved December 22, 1994, for thromboprophylaxis in abdominal surgery for patients at risk for thromboembolic complications. Fragmin is also indicated for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery who are at risk for thromboembolic complications. In May 1999, Fragmin was approved for prophylaxis of ischemic complications in unstable angina and non-q-wave myocardial infarction, when concurrently administered with aspirin therapy.

The sponsor has conducted the trial entitled, "Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism." (also known as the CLOT trial). The original protocol was submitted October 13, 1999. DGICDP provided comments on February 16, 2000.

MEETING OBJECTIVE:

To discuss questions posed by Pharmacia and Upjohn in the background package dated November 11, 2002 (received November 12, 2002), submitted to NDA 20-287 for a proposed indication for Fragmin (dalteparin sodium) Injection for extended prophylaxis of recurrent DVT and/or PE in patients with cancer. The sponsor seeks to submit the supplemental NDA (sNDA) in a Common Technical Document (CTD) format.

Questions: (background package submitted November 11, 2002, received November 12, 2002)

In response to the firm's questions in their November 11, 2002 submission (received November 12, 2002) the following agreements were reached after discussion. The form provides the firm's questions, followed by the Agency's responses in bolded lettering.

Question 1.
Dalteparin is a Low Molecular Weight Heparin (LMWH) with a well-characterized mechanism of action and an established role in anticoagulant therapy in multiple treatment settings. The CLOT Study 98-FRAG-069, sponsored by Pharmacia, is a large, phase III, randomized trial comparing dalteparin (FRAGMIN) to oral anticoagulation for the prevention of recurrent thrombosis in cancer patients. The primary, intention-to-treat analysis, has demonstrated a highly statistically significant advantage (Hazard Ratio 0.48, p=0.0017) for dalteparin over an active control (oral anticoagulant therapy) in the reduction of venous thromboembolism (VTE) recurrence in cancer patients. In addition, Study 98-FRAG-069 has confirmed the safety of long-term dalteparin therapy.

Given the large body of knowledge regarding use of dalteparin and the highly positive findings in Study 98-FRAG-069, can this trial serve as the basis for approval of a sNDA for the proposed additional

indication for FRAGMIN Injection: The extended prophylaxis of recurrent deep vein thrombosis and/or pulmonary embolism in patients with cancer and symptomatic VTE?

FDA Response:

No, this trial can not serve as the basis for approval of a sNDA for the proposed indication. More data are needed.

- **Provide data to support that Fragmin is safe and effective in the treatment of acute pulmonary embolism (PE). There was no active control for treatment of PE. There were more than 30% of patients with acute PE at the time enrollment. Neither Fragmin nor oral anti-coagulant (OAC) therapy (or their combination) has been shown effective and safe for the treatment of acute PE. The results cannot be interpreted using Fragmin in both the study and control groups.**

- **Provide data to support that Fragmin is safe and effective in the treatment of acute deep vein thrombosis (DVT). There was no active control for the treatment of DVT in this trial. Neither Fragmin nor OAC alone (or in combination) has been shown effective and safe for treatment of acute DVT. The results cannot be interpreted using Fragmin in both the study and control groups in the initial period of treatment.**

- **Provide follow-up data for both primary and secondary endpoints (6-9 months).**

- **The acceptance of the single study as a sufficient scientific and regulatory basis for approval of Fragmin for the new indication will be determined by its adequacy to support the efficacy claim based on strength of the results (see *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products,* May 1998).**

Question 2.:

The proposed sNDA is for a new indication and, therefore, Pharmacia will limit efficacy data in the submission only to the study supporting the new indication.

Is this approach acceptable to the Division?

FDA Response:

- **No, provide all data which relate to the treatment of acute DVT or PE using Fragmin, and all data that relate to long-term (> 1 month) Fragmin alone therapy in any patients.**

- **Provide discussion and summary if studies are not done by Pharmacia.**

Question 3.

This drug has been marketed for approximately 8 years in the USA and safety updates have been provided to the Agency on a regular basis. We plan to include safety information collected solely from the CLOT Study in support of this indication.

Does your Division agree?

FDA Response:

No. Provide all safety information that relate to the treatment of acute DVT or PE, and all data that relate to long-term (> 1 month) therapy in all studies including literature summaries. There are no safety data available so far regarding Fragmin in the treatment of DVT and/or PE, for long-term use.

Question 4.

The Statistical Analysis Plan is provided in Appendix 4. An example of data displays can be provided as soon as they are available and discussed, if desired, at a time that is suitable for the Division.

Is this approach acceptable to your Division?

FDA Response:

The approach is acceptable.

Question 5.

We propose to submit electronic case report tabulations (CRTs) including all data collected and calculated variables used in the analyses as SAS export files. No individual patient profiles either as paper copy or as PDF files is planned.

Does your Division agree?

FDA Response:

No. Provide individual patient profiles in electronic or paper form.

Question 6.

The FDA approved Dalteparin sodium approximately 8 years ago (NDA: 20-287). During the course of development of this drug, Pharmacia conducted a comprehensive nonclinical pharmacology/toxicology, chemistry and manufacturing and control, and clinical pharmacokinetic/pharmacodynamic program. As there is no change in the formulation for the proposed sNDA and:

a. The nonclinical pharmacology/ ADME/Toxicology of dalteparin sodium is well known.
b. The pharmacokinetic/pharmacodynamic profiles of dalteparin sodium are well known.
c. The Chemical Manufacturing and Control information for dalteparin sodium is well established, hence, CMC information will not be included in the sNDA.

Pharmacia, therefore, proposes to include in the sNDA only an overview for the above mentioned sections "a" and "b" with reference made to NDA 20-287 dalteparin injection along with relevant new information as appropriate from results of new studies and review of literature since the last submission.

Does the Division agree with this approach?

FDA Response:

Yes.

Question 7.

The sNDA will be submitted in the Common Technical Document format on CD-ROM.

Is this approach acceptable to the Agency? Does the Division have special requirements for a sNDA submitted in CTD format?

FDA Response:

The Division requests that a paper copy of the clinically-related sections be provided for the medical reviewer and a paper copy of the pharmacology section be provided for the pharmacology reviewer.

Please provide three extra copies of the summary sections.

Question 8.

The proposed new indication for FRAGMIN Injection has a rare occurrence in the pediatric population. Recently published clinical data indicate the majority of pediatric venous thrombosis occur in the upper venous system frequently in association with central venous catheters (Massicotte, 2001). The reduced incidence of the disease of interest (lower limb, proximal DVT and/or PE), combined with the relative rarity of childhood cancer makes clinical trials impractical. In accordance with (b) (4)

Action Items:

- The sponsor will provide additional data from other studies using Fragmin to support the safety and efficacy of Fragmin in acute VTE and PE patients and the proposed dosage strength for long-term use of FRAGMIN in cancer patients with VTE in a briefing document for further discussion and for inclusion in the sNDA.

- The sponsor will provide literature references from historical trials to support the proposed indication of short-term anticoagulation with FRAGMIN in cancer patients with acute VTE and PE in a briefing document for further discussion and for inclusion in the sNDA

- The sponsor will request a pre-sNDA meeting for this indication in the future.

{See appended electronic signature page} *{See appended electronic signature page}*

Signature, recorder Signature, Chair

drafted: dm/12/9/02
revised: J.DuBeau 12.16.02
initialed: J.DuBeau 12.16.02/R.Justice 1.7.03
Finalized: January 8, 2003
Filename: N20287MM121202.doc

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
1/8/03 12:54:50 PM

Robert Justice
1/8/03 02:03:40 PM

cc
olivey

IND 25,924

Pharmacia & Upjohn Company
Attention: Ms. Leslie Franks
7000 Portage Road
Kalamazoo, Michigan 49001

FEB 16 2000

Dear Ms. Franks:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium injection).

We also refer to you submission dated October 13, 1999, serial number N-143, containing a new protocol entitled: "Randomized Comparison of Low Molecular Weight Heparin versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients with Venous Thromboembolism (CLOT in Cancer Patients)."

We have completed the review of your submission, and have the following comments and recommendations:

1. Consider using an approved regimen of enoxaparin or heparin for the initial treatment of VTE in the control group. In the proposed study, using Fragmin as the initial treatment of VTE in both treatment and control groups may complicate interpretation of the study results.

2. Record all adverse events in the Case Report Form (CRF) including grade 1 (mild) and grade 2 (moderate) events. A secondary analysis of only the severe events (grade 3 and 4) may be done.

3. Adverse events meeting serious adverse event criteria but representing a relapse or an expected change or progression of baseline malignancy should still be considered as serious adverse events. A secondary analysis of serious adverse events excluding these disease-related events may be done.

4. Clarify the phrase "new, symptomatic, objectively documented DVT, PE" in the secondary outcomes section. Specify the criteria that will be used to define these events.

5. To minimize potential bias, the reader of the venogram, ultrasound and V/Q scans should be blinded to patient treatment assignment and also should be the same person at baseline as at follow-up for each patient.

6. Provide the rationale for "allowing a suitable lag time" in time-to-event analysis for patients who discontinued drug permanently and specify how long the lag time will be and how this will be determined.

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

Sincerely yours,

4 2-16-00

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

cc:
Orig IND 25,924
HFD-180/Div.File
HFD-180/L.Talarico
HFD-180/M.Liu
HFD-180/K.Oliver
HFD-180/K.Robie-Suh 02/16/00
R/D init: L.Talarico 02/16/00
Draft: KO/February 16, 2000 KOliver 02/16/00
Final: KO/02/16/00/c:\mydocuments\IND24924-02-16-00-IR

INFORMATION REQUEST (IR)

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

Diane Leaman 2/10/06

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

Diane Moore 12/2/04

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Application Integrity Policy

The Application Integrity Policy (AIP) has not been invoked for this NDA or this NDA sponsor.

Diane Seaman
4/23/07

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Application Integrity Policy

The Application Integrity Policy (AIP) has not been invoked for this NDA or this NDA sponsor.

Diane Moore 12/2/04

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

CAC/ECAC Report

No CAC/ECAC report was needed for this NDA supplement.

Diane Leam 4/23/07

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

CMC Review

CMC review completed 12/2/04. No CMC review is needed for Cycle 3.

Diane Leamon
1/23/05

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Controlled Substance Staff Reviews

This product does not require a Controlled Substance Staff review.

Diane Moore 12/2/04

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Demographic Worksheet

No demographic worksheet was generated for this supplemental application.

Diane Leam
4/23/07

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

EER

The EER Evaluation Report is still acceptable per Dr. Liang Zhou, April 27, 2007. The establishment was evaluated for a subsequent application and found acceptable.

Diane Leamon 4/27/07

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Environmental Assessment

A categorical exclusion is claimed for this NDA in accordance with 21 CFR part 25.31 (b), as amended in the 29-Jul-1997 Federal Register. This was found to be satisfactory (see page 5, Chemistry Review, dated December 2, 2004, by Dr. Al Al-Hakim).

Diane Leamas
4/23/07

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Federal Register Notices

This application was not the subject of any Federal Register Notices.

Diane Moore 12/2/04

Memo from DSI regarding GLP inspection (if any)

No GLP inspection was needed from DSI for this drug product.

Diane Leamon
4/23/07

Methods Validation

Methods validations have been reviewed and found acceptable (see page 3 of CMC review by Dr. Ali Al-Hakim dated December 2, 2004).

Diane Leam
9/23/07

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Microbiology Review

No microbiology review for efficacy is required for this application.

Diane Moore
12/13/04

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Pharmacology/Toxicology review(s) and Memoranda

No relevant pharmacology and toxicology information has been submitted in this supplement. Information submitted in the original submission and subsequent amendments has already been reviewed.

Dennis Leaman
4/23/07

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Post-marketing Commitments

There were no post-marketing commitments made for this drug product.

Diane Seaman 2/10/06

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Post-marketing Commitments

There were no post-marketing commitments made for this drug product.

Diane Moore 12/2/04

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Risk Management Plan

This application does not require a risk management plan. No risk management plan was developed for this supplement.

Diane Seamon
4/23/07

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Risk Management Plan

This application does not require a risk management plan. No risk management plan was developed for this supplement.

Diane Leaman 2/10/06

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Risk Management Plan

This application does not require a risk management plan. No risk management plan was developed for this supplement.

Deane Moore 12/2/04

NDA 20-287/S-035 Cycle 3
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Safety Update Review

The safety update is included on pages 3 and 4 in the Medical Officer review dated April 23, 2007.

Diane Leaver
4/23/07

Statistical Review(s) of Carcinogenicity Studies

A Pharmacology review for carcinogenicity studies is not required for this supplement.

Diane Lean
4/23/07

NDA 20-287/S-035
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Statistics review(s) and memoranda regarding dissolution and/or stability

The chemistry, manufacturing and controls information is not changed. A statistical review of drug stability is not needed for this supplemental application.

Diane Moore 12/9/04

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 20-287	BLA STN# NDA Supplement # 035	If NDA, Efficacy Supplement Type SE-1	
Proprietary Name: Fragmin® Established Name: dalteparin sodium Dosage Form: injection		Applicant: Pharmacia & Upjohn Company	
RPM: Diane Leaman		Division: DMIHP (HFD-160)	Phone # (301) 796-1424

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: X☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	May 1, 2007
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE January 14, 2005 NA March 14, 2006
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP	☐ Yes X No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As X Other Burst

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	X Included
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

If "Yes," skip to question (4) below. If "No," continue with question (2).

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	–
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	DD 4/30/07; TL 4/30/07; DDD 3/13/06; TL 3/13/06; DDD 1/14/05; TL 1/14/05 DD 4/29/07; TL 4/26/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	4/30/07
• Original applicant-proposed labeling	9/14/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Lovenox 5/18/04; Arixtra 5/28/04; Argatroban 10/29/03; Refludan 4/2/03; Angiomax 6/10/02
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	4/30/07

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	x DMETS 4/12/07; 3/14/06 ☐ DSRCS x DDMAC 11/23/04 ☐ SEALD X Other reviews 45/1/07; 4/2/07 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	Filing Rev 5/3/04
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	N/A
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	4/24/07
• Incoming submission documenting commitment	4/26/07
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Letters: 4/19/07; 3/9/07; 4/18/06; 4/14/06; 1/24/06; 11/14/05; 11/4/05; 3/29/05; 5/3/04; 3/29/04 Faxes: 4/24/07; 6/1/06; 3/7/06; 2/7/06; 1/30/06; 4/18/05; 1/7/05 Telecon: 4/30/07
❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 10/28/03
• EOP2 meeting *(indicate date)*	☐ No mtg 12/11/02
• Other (e.g., EOP2a, CMC pilot programs)	6/13/06; 5/2/06; 3/7/06; 2/24/06; 2/7/06; 4/19/05; 1/14/05; 1/11/05
❖ Advisory Committee Meeting	☐ No AC meeting
• Date of Meeting	9/6/06
• 48-hour alert or minutes, if available	9/6/06
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	8/1/06

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	12/2/04
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	X None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion *(indicate review date)(all original applications and*	CMC review 12/2/04

• ☐ Review & FONSI *(indicate date of review)*	N/A
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	4/18/07; 1/7/05; 1/4/05; 4/18/07 ☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 9/24/04 X Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	X None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	4/26/07; 4/24/07; 3/13/06; 1/14/05
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Mo review 1/14/05
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	X None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	X Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	4/23/07 MO review
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	X Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	12/15/04 rev; 2/4/05 and 10/23/03 letters
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 4/25/07; 12/3/04
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/29/04

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 20-287	BLA STN# NDA Supplement # 035	If NDA, Efficacy Supplement Type SE-1	
Proprietary Name: Fragmin® Established Name: dalteparin sodium Dosage Form: injection		Applicant: Pharmacia & Upjohn Company	
RPM: Diane Leaman		Division: DMIHP (HFD-160)	Phone # (301) 796-1424

NDAs: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: X☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	May 1, 2007
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE January 14, 2005 NA March 14, 2006
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP	☐ Yes X No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As X Other Burst

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	X Included
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires: -
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below* (Summary Reviews).

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below* (Summary Reviews).

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below* (Summary Reviews). *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	DD 4/30/07; TL 4/30/07; DDD 3/13/06; TL 3/13/06; DDD 1/14/05; TL 1/14/05 DD 4/29/07; TL 4/26/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	4/30/07
• Original applicant-proposed labeling	9/14/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Lovenox 5/18/04; Arixtra 5/28/04; Argatroban 10/29/03; Refludan 4/2/03; Angiomax 6/10/02
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	4/30/07

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	x DMETS 4/12/07; 3/14/06 ☐ DSRCS x DDMAC 11/23/04 ☐ SEALD X Other reviews 45/1/07; 4/2/07 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	Filing Rev 5/3/04
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	N/A
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	4/24/07
• Incoming submission documenting commitment	4/26/07
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Letters: 4/19/07; 3/9/07; 4/18/06; 4/14/06; 1/24/06; 11/14/05; 11/4/05; 3/29/05; 5/3/04; 3/29/04 Faxes: 4/24/07; 6/1/06; 3/7/06; 2/7/06; 1/30/06; 4/18/05; 1/7/05 Telecon: 4/30/07
❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 10/28/03
• EOP2 meeting *(indicate date)*	☐ No mtg 12/11/02
• Other (e.g., EOP2a, CMC pilot programs)	6/13/06; 5/2/06; 3/7/06; 2/24/06; 2/7/06; 4/19/05; 1/14/05; 1/11/05
❖ Advisory Committee Meeting	☐ No AC meeting
• Date of Meeting	9/6/06
• 48-hour alert or minutes, if available	9/6/06
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	8/1/06
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	12/2/04
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	X None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion *(indicate review date)(all original applications and*	CMC review 12/2/04

• ☐ Review & FONSI *(indicate date of review)*	N/A
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	4/18/07; 1/7/05; 1/4/05; 4/18/07 ☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 9/24/04 X Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	X None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	4/26/07; 4/24/07; 3/13/06; 1/14/05
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Mo review 1/14/05
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	X None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	X Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	4/23/07 MO review
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	X Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	12/15/04 rev; 2/4/05 and 10/23/03 letters
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 4/25/07; 12/3/04
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/29/04

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 20-287	BLA STN# NDA Supplement # 035	If NDA, Efficacy Supplement Type SE-1	
Proprietary Name: Fragmin® Established Name: dalteparin sodium Dosage Form: injection		Applicant: Pharmacia & Upjohn Company	
RPM: Diane Leaman		Division: DMIHP (HFD-160)	Phone # (301) 796-1424

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: X☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	May 1, 2007
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE January 14, 2005 NA March 14, 2006
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP	☐ Yes X No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As X Other Burst

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	X Included
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below* (Summary Reviews)).	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	DD 4/30/07; TL 4/30/07; DDD 3/13/06; TL 3/13/06; DDD 1/14/05; TL 1/14/05 DD 4/29/07; TL 4/26/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	4/30/07
• Original applicant-proposed labeling	9/14/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Lovenox 5/18/04; Arixtra 5/28/04; Argatroban 10/29/03; Refludan 4/2/03; Angiomax 6/10/02
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	4/30/07

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	x DMETS 4/12/07; 3/14/06 ☐ DSRCS x DDMAC 11/23/04 ☐ SEALD X Other reviews 45/1/07; 4/2/07 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	Filing Rev 5/3/04
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	N/A
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	4/24/07
• Incoming submission documenting commitment	4/26/07
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Letters: 4/19/07; 3/9/07; 4/18/06; 4/14/06; 1/24/06; 11/14/05; 11/4/05; 3/29/05; 5/3/04; 3/29/04 Faxes: 4/24/07; 6/1/06; 3/7/06; 2/7/06; 1/30/06; 4/18/05; 1/7/05 Telecon: 4/30/07
❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 10/28/03
• EOP2 meeting *(indicate date)*	☐ No mtg 12/11/02
• Other (e.g., EOP2a, CMC pilot programs)	6/13/06; 5/2/06; 3/7/06; 2/24/06; 2/7/06; 4/19/05; 1/14/05; 1/11/05
❖ Advisory Committee Meeting	☐ No AC meeting
• Date of Meeting	9/6/06
• 48-hour alert or minutes, if available	9/6/06
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	8/1/06
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	12/2/04
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	X None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion *(indicate review date)(all original applications and*	CMC review 12/2/04

• ☐ Review & FONSI *(indicate date of review)*	N/A
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	4/18/07; 1/7/05; 1/4/05; 4/18/07 ☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 9/24/04 X Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	X None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	4/26/07; 4/24/07; 3/13/06; 1/14/05
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Mo review 1/14/05
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	X None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	X Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	4/23/07 MO review
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	X Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	12/15/04 rev; 2/4/05 and 10/23/03 letters
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 4/25/07; 12/3/04
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/29/04