FDA Advisory Committee Briefing Document
Prepared by the Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
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Fragmin® (dalteparin sodium injection)
NDA # 20-287; Sponsor: Pfizer, Inc.
A supplemental application for a new indication

Contents

Executive Summary

Introduction

Fragmin is a low molecular weight heparin drug first approved in 1994. This approval was for use of the drug as thromboprophylaxis among abdominal surgery patients at risk for thromboembolic complications. Subsequent approvals were for thromboprophylaxis in other clinical settings. This Oncologic Drugs Advisory Committee is convened to discuss the clinical data supporting a supplemental application related to the use of Fragmin in the treatment of venous thromboembolism (VTE) among patients with cancer.

Data from a single, open label clinical study (referred to as the "CLOT" study) were submitted to FDA in support of the new indication. The CLOT study randomized cancer patients with symptomatic VTE to one of two regimens: 1) an initial 5-7 days of Fragmin plus oral anticoagulant (OAC) followed by OAC alone for a total of 6 months or 2) to a month of Fragmin at a relatively high dose followed by continued Fragmin administration at a lower dose for the next 5 months. Several aspects of the submitted clinical data present unique considerations related to data interpretation and potential market approval for treatment of VTE in the "cancer patient." Specifically, the following considerations are highlighted for discussion:

- Limitations of the clinical data:
  Date from a single clinical study (The CLOT study) forms the definitive evidence of safety and efficacy for the proposed indication.

- CLOT efficacy findings:
  Competing risks (death and recurrent VTE) and possible informative censoring impact interpretation of the CLOT findings. Patients in the study were assigned to treatment regimens for six months. However, approximately half the patients did not complete the full duration of the assigned study treatment, including approximately 40% of the patients who died during the six month study period. Other challenges in data interpretation relate to differences in patient management between the two study groups due to differences in the study agent administration routes (oral versus subcutaneous injection) and the need for regular international normalized ratio (INR) blood monitoring in only one study group.

- CLOT safety findings:
  Although overall-mortality findings were similar between the two study groups, study drug discontinuation due to death was approximately twice as common among patients receiving Fragmin as among patients treated with OAC. Other safety findings related to the rates of major hemorrhage, thrombocytopenia and liver enzyme elevation.

- Proposal for "extended" use of Fragmin:
  CLOT provided evidence that, compared to OAC, Fragmin administration decreased recurrent VTE over a six month period of time. However, essentially all the treatment benefit was evidenced during the first month of therapy. After the first month, VTE recurrence rates were similar between the two study groups.

- Implications for VTE treatment in the general population:
  Fragmin is not approved for the treatment of VTE in any population. The submitted clinical data are obtained from its use in "cancer patients." Market approval solely for use among cancer patients may have implications for similar usages among patients without cancer—a situation in which the CLOT study findings may not fully predict the risks and benefits of the treatment usage. This consideration may impact the proposed package insert and have implications for a "non-cancer patient" clinical development program.

Background

Proposed indication:

The sponsor proposes the following new indication for Fragmin: "for the extended treatment of symptomatic VTE (proximal DVT and/or PE) to prevent recurrent VTE in patients with cancer." (DVT = deep vein thrombosis; PE = pulmonary embolus)

The Fragmin dosage proposed for the new indication is 200 IU/kg SC once daily for the first month followed by 150 IU/kg SC once daily for the next five months, for a total of six months of treatment. As summarized below, the proposed Fragmin dosage regimen differs from the currently approved regimens.

Fragmin is currently approved for the following indications:

- Thromboprophylaxis in abdominal surgery for patients at risk for thrombotic complications. (maximum dosage 5000 IU SC daily for up to 10 days)

- Prophylaxis of deep vein thrombosis (DVT) in patients undergoing hip replacement surgery who are at risk for thromboembolic complications. (maximum dosage 5000 IU SC daily for up to 14 days)

- Prophylaxis of ischemic complications in unstable angina and non-Q wave myocardial infarction when concurrently administered with aspirin therapy. (maximum dosage 10000 IU SC every 12 hours for up to 8 days, with aspirin)

- Prophylaxis of DVT which may lead to pulmonary emboli (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness. (maximum dosage 5000 IU SC daily for up to 14 days).

Antithrombotic drug considerations:

The antithrombotic treatment of VTE may be categorized as either:

- "Prophylaxis:" a primary preventive treatment in which patients at risk for VTE are administered the antithrombotic drug to prevent VTE.

- "Treatment:" a secondary preventive treatment in which patients who have VTE receive the antithrombotic drug to prevent extension of the blood clot or recurrence of a blood clot.

Currently approved antithrombotic drug dosage regimens vary according to whether the usage is for VTE prophylaxis or treatment. These variations of drug regimen are necessary due to the differing risks and benefits in the two clinical settings. In general, greater anticoagulant bioactivity is necessary for VTE treatment (generally higher drug dosages) than that for VTE prophylaxis. Concomitant with the greater anticoagulation, the risks for bleeding generally increase. Fragmin currently is approved for VTE prophylaxis—not for VTE treatment. The proposed indication under consideration is for the use of Fragmin as a VTE treatment specifically among cancer patients.

The following drugs are approved for use in the prophylaxis (primary prevention in specific patient populations, generally as defined in each label) of VTE, as follows:

- Fragmin® injection (Dalteparin sodium injection)
- Lovenox® (Enoxaparin sodium injection)
- Arixtra® (Fondaparinux sodium injection) with warfarin
- Warfarin
- Unfractionated heparin

The following drugs are approved for VTE treatment (in the broad population of patients with VTE):

- Unfractionated heparin with warfarin
- Lovenox® (Enoxaparin sodium injection) with warfarin
- Innohep® (Tinzaparin sodium injection) with warfarin
- Arixtra® (Fondaparinux sodium injection) with warfarin

During VTE treatment, warfarin administration is generally continued for several months following the acute antithrombotic therapy. During this time period, warfarin administration requires the regular monitoring of blood coagulation tests. Consequently, an importance advance in VTE treatment would be the availability of a safe and effective "long term" anticoagulation regimen that does not require the regular monitoring of blood coagulation tests.

Among the antithrombotic drugs listed above, three are forms of low molecular weight heparin (Innohep, Lovenox and Fragmin). None of these low molecular weight (LMW) heparin drugs are approved for administration in an "extended" or "long term" manner. In general, the LMW heparin drugs are approved for usage over 14 days or less, with an exception relating to the use of Lovenox in VTE prophylaxis among hip surgery patients (approximately 35 days).

The data to support the VTE treatment indication for the most recently approved antithrombotic drugs (Lovenox, Arixtra, Innohep) consisted of clinical findings from at least two confirmatory clinical studies . Historically extensive clinical experience with unfractionated heparin and warfarin has established the utility of these two drugs in VTE treatment.

Consequently, the potential market approval of Fragmin for the proposed indication might present several notable observations, as follows: the first "extended" usage of a LMW heparin drug; the first extended duration regimen that obviates the need for regular

blood coagulation test monitoring; the first approval of an antithrombotic drug specifically for "cancer patients;" and a VTE treatment approval where a single clinical study provided the definitive evidence of safety and efficacy.

Fragmin supplement regulatory history:

March 16, 2004	Submission of supplement to FDA.
January 14, 2005	FDA issued a letter requesting additional safety analyses and the performance of certain post-marketing clinical studies.
September 14, 2005	Submission of response to FDA letter.
March 15, 2006	FDA issued a letter requesting at least one additional clinical study to provide definitive evidence of the safety and efficacy for the proposed indication.

Subsequent to the March 15, 2006 FDA letter, the sponsor submitted additional analyses of findings from the CLOT study that are subsumed within the current discussion topics for the Committee.

Regulatory considerations:

The usual FDA requirement for more than one adequate and well controlled confirmatory clinical study to provide substantial evidence of safety and efficacy reflects the need for independent substantiation of experimental results. These observations are detailed within the guidance document entitled, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," available at the internet address of: http://www.fda.gov/cder/guidance/1397fnl.pdf.

As outlined in the "Effectiveness" guidance document, a single clinical study may sometimes supply sufficient evidence of safety and efficacy if the single study's findings are supported by findings from other, related clinical studies. For example, one consideration applicable to the current Fragmin supplement proposal is the consideration of the VTE prophylaxis clinical studies as supportive evidence from a related indication that may be sufficient to support the CLOT study's findings. FDA has concerns regarding the persuasiveness of the CLOT study findings, even when considered in the context of the VTE prophylaxis studies.

The "Effectiveness" guidance document also notes that FDA may regard a single clinical study as providing sufficient evidence of safety and efficacy in a unique situation where the study findings are robust, persuasive and the treatment effect is so clinically important that conduct of another study would be regarded as unethical. FDA does not regard the CLOT study findings as prohibitive to the conduct of another clinical study.

The CLOT Study

Title: Randomized Comparison of Low-Molecular Weight Heparin versus Oral Anticoagulation Therapy for Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism (CLOT study)

Design: Randomized, open label, multinational study in which cancer patients presenting with VTE were randomized to one of two treatment regimens:

> -the oral anticoagulant ("OAC") regimen: Fragmin at 200 I.U./kg SC daily (max 18,000 IU) for five to seven 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 six months. The OAC consisted of either warfarin or acenocoumarol.
>
> -the "Fragmin®" regimen: Fragmin at 200 IU/kg (max 18,000 IU) SC daily for one month and then a dose of 150 IU/kg (max 18,000 IU) SC daily for the remaining five months of treatment.

Treatment continued until the occurrence of VTE, the occurrence of an unacceptable toxic/adverse event, physician or patient decision to discontinue therapy, or when the six month treatment was completed.

FDA review team comments: Use of Fragmin for the first week of the OAC regimen represents a non-approved use and the extent to which this usage is accepted as a standard therapy is unclear. Nevertheless, the study was designed as a test of the investigational treatment's superiority over the control treatment and in this analytical context, the control treatment regimen was regarded as reasonable.

Patients were assessed at scheduled clinic visits at the following time points: day 7 to 10; and the ends of month 1, month 3 and month 6. 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 also asked about their general health, including any signs or symptoms of VTE recurrence or central venous thrombosis (CVT), bleeding or other adverse events. If there was a suspected thrombosis, the patient underwent investigation according to pre-defined algorithms. Following completion of the six month study, patients were followed for survival for an additional six months. Some patients could continue Fragmin for up to 12 months (an uncontrolled portion of the study).

The study's primary endpoint was a comparison of the time to recurrence of VTE. The VTE recurrence was determined following adjudication by a Central Adjudication Committee that was blinded to treatment assignment. Secondary endpoints were comparisons of bleeding rates; comparisons of the occurrence of DVT, PE or CVT of the upper limb(s), neck or chest; and comparison of death rates.

FDA review team comments: As summarized below, two alterations of the study design and conduct are notable, especially in light of the open label nature of the study. The submitted information indicates that the alterations were performed without comparisons of interim results between the two study groups.

- *Redefinition of the primary endpoint: The study began on May 3, 1999. The primary efficacy endpoint was redefined on September 13, 1999 from comparisons of recurrent VTE and major bleeding (co-primary endpoints) to recurrent VTE alone. With a data cut-off of August 31, 1999, 34 patients were enrolled. FDA analysis of the number of patients who had major bleeding among these first 34 patients showed that the Fragmin group had higher major bleeding (3/17 = 18%) compared to the OAC group (0/17 = 0%).*

- *Re-estimation of the sample sizes: The original protocol targeted the enrollment of 474 patients. The protocol was subsequently amended to target enrollment of 586 patients (based upon the use of a log rank analysis for the power calculation instead of a Fisher's exact test) and to include an upward adjustment of the 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 inconclusive. A second blinded review was planned by the Steering Committee and was performed in January, 2001. At this time, analyses indicated that an increase in total sample size from 586 patients to 676 patients would likely satisfy the 85% power requirement. Consequently, a protocol amendment introduced a further sample size adjustment upward to 676 patients, in order to increase the probability of reaching the targeted number of primary events.*

Randomization and baseline characteristics:

Overall, 677 patients were randomized. One patient did not provide consent and was excluded from the study analyses. Three of the remaining 676 "intent to treat" patients did not receive the assigned study treatment. Hence, the "as treated" population consists of 673 patients.

Baseline characteristics and prognostic factors were balanced between both arms (see Appendix). Most patients had solid tumors (90%) and stage IV disease (75%). The distribution of tumor types was similar in the arms of the study, with the most common primary histology consisting of breast, gastrointestinal and lung cancers. At entry, the qualifying VTE event in about 2/3 of patients was symptomatic proximal DVT while 1/3 had both symptomatic proximal DVT and PE or PE alone.

Disposition:

By six months, approximately half of the patients in each study arm had discontinued the assigned study treatment, with death as the most common basis for treatment discontinuation. Approximately 40% of the patients were dead by six months. A notable reason for discontinuation of the assigned study treatment regimen was the occurrence of recurrent VTE. These observations illustrate the extent of the competing risks of VTE and death.

Approximately twice as many patients discontinued Fragmin (17%) due to death as compared to patients receiving OAC (7%). Conversely, approximately twice as many OAC patients (14%) discontinued the assigned treatment due to recurrent VTE as compared to Fragmin patients (6%).

The sponsor summarized the reasons for discontinuation of the assigned study treatment agent in the following table.

Table 1. Reasons for Study Drug 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

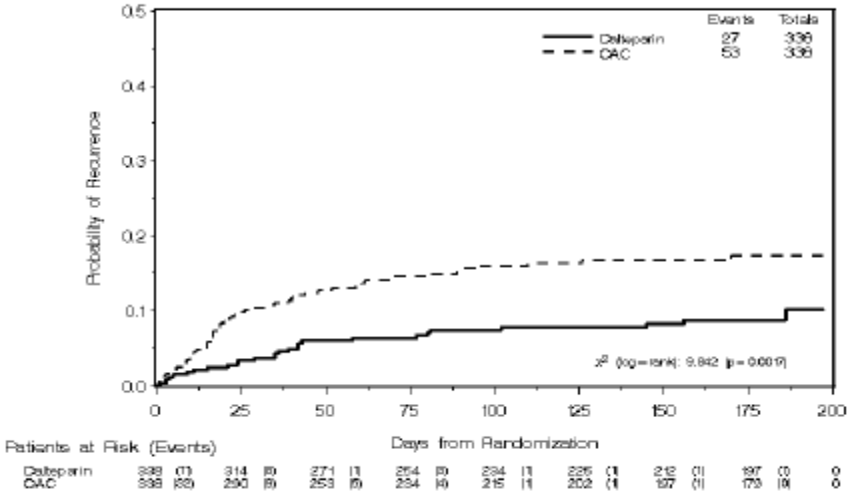
Efficacy findings:

Overall, 27 of 338 (8%) patients randomized to Fragmin and 53 of 338 (15.7%) patients randomized to OAC experienced at least one adjudicated, symptomatic VTE during the six month study (primary endpoint: log rank test, p = 0.0017). As shown below in the table and figure, the treatment benefit was largely related to reduction in the recurrence rate during the first month of the study agent administration (the time period for the higher Fragmin dose administration).

Table 2. Patients with First Recurrent VTE, by Week

Period	Fragmin n = 338	OAC n = 338
Weeks 1 - 4	11 (3%)	33 (10%)
Weeks 5 - 28	16 (5%)	20 (6%)
Total	27 (8%)	53 (16%)

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



FDA Review Team Comments: While the CLOT study demonstrated a treatment effect in favor of Fragmin, reliance upon this single study finding as definitive evidence of efficacy should be considered within the context of the limitations of the study design, conduct and findings. The following considerations call the robustness of the primary endpoint into question:

- *Competing risks of death and VTE and the potential inaccuracy in VTE diagnosis at the time of death*
- *Inconsistencies in primary endpoint exploratory subsets, especially the non-metastatic cancer population*

<u>Competing risks of death and VTE and the potential inaccuracy in VTE diagnosis at the time of death:</u>

Perhaps as a consequence of enrollment of a predominance of patients with advanced cancer, the death rate (268/676, 40%) was substantially greater than the recurrent VTE rate (80/676, 12%) in the entire CLOT study population. Death and recurrent VTE are not independent events (death reduces the risk of subsequent VTE to zero). Consequently, the primary endpoint outcome of recurrent VTE is susceptible to misinterpretation due to the competing risk of death. As has been previously noted, when two failure processes such as death and VTE recurrence affect a patient population, one may not obtain unbiased estimates of the risk for one cause (recurrence of VTE) by censoring other events (such as death).[1]

The primary endpoint event of recurrent VTE is vulnerable to errors in ascertainment when a death is accompanied with VTE (as may occur in the advanced cancer setting).

[1] Piantadosi; Clinical Trials, 1997, Wiley, page 136.

Death causality was determined in the CLOT study by a Central Adjudication Committee that was blinded to treatment assignment. The Committee was charged with assigning deaths to one of four categories: underlying cancer; fatal PE; fatal hemorrhage; other.

Of the 268 deaths, all but 25 cases were attributed to the underlying cancer. Fatal PE was assessed as the cause of death in 6 Fragmin patients and 8 OAC patients. The relatively few cases of fatal PE may relate to the rarity of the event or the inability to ascertain the occurrence of PE at the time of death. Limitations in the ascertainment of PE at the time of death may have importantly impacted the CLOT study findings since the overall risk for death was more than three times greater than the detected risk for recurrent VTE. Table 3 explores this consideration.

Table 3. Death and VTE Recurrence, in Mutually Exclusive Categories

Outcome	Fragmin n = 338	OAC n = 338
Died but did not have recurrent VTE	111 (33%)	97 (28%)
Had recurrent VTE and then died	20 (6%)	40 (12%)
Had recurrent VTE and survived	7 (2%)	13 (4%)
None of the above	200 (59%)	188 (56%)

Table 3 shows that the major differences between the study groups mainly relates to two observations:

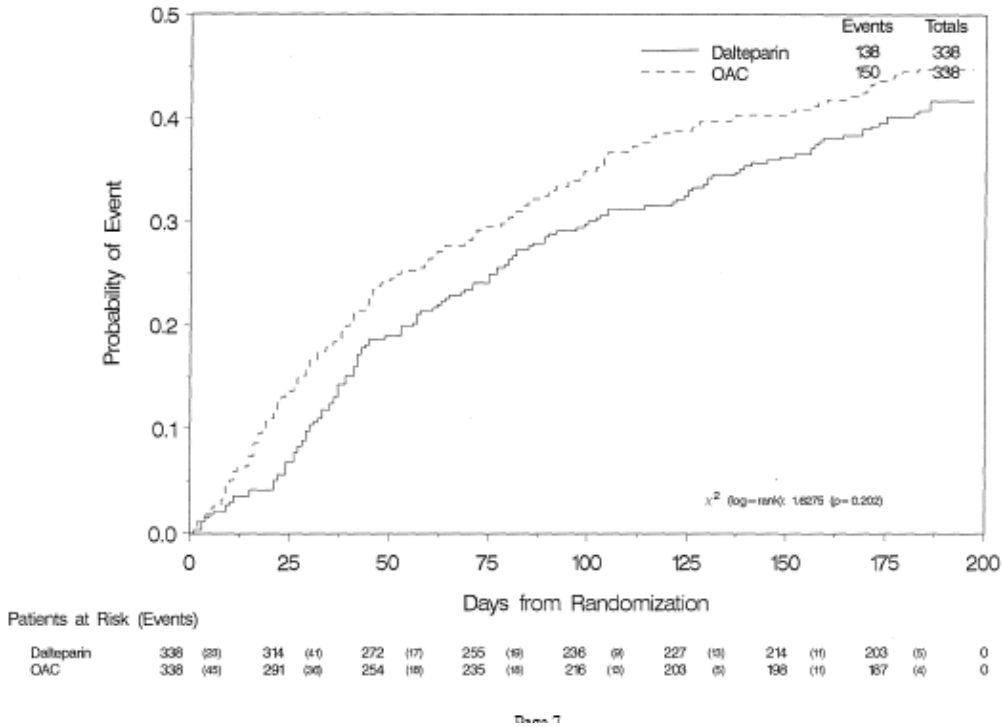
- *a favorable Fragmin effect among patients who had recurrent VTE and then died*
- *an unfavorable Fragmin effect among patients who died without recurrent VTE.*

Due to these opposing observations, inaccuracy in the diagnosis of VTE at the time of death may importantly limit the robustness of the primary endpoint result. Table 3 also illustrates the limitations associated with reporting only the total mortality and the percent recurrent VTE at any time. This type of reporting leads to the conclusion that Fragmin reduces the risk of recurrent VTE regardless of the risks for mortality. This conclusion does not indicate the limitations associated with the competing risks of death and recurrent VTE. For example, this conclusion does not convey the observation that similar percentages of CLOT patients experienced neither of the two competing events.

Given that that death and recurrence of VTE may not be independent events, as well as the potential difficulty in assessing VTE at the time of death, a combination of all cause mortality with recurrent VTE in a composite exploratory endpoint is useful because VTE-free survival is not subject to as many biases and is clinically meaningful.

The following survival curve below shows the VTE-free survival of the two treatment groups. The difference is not significant (log-rank p = 0.2).

Figure F2.1 Time to First VTE at 6 Months and/or Death at 6 Months
(Intent–To–Treat) – Kaplan–Meier Curves



Further sensitivity analyses of time to treatment failure (defined as first recurrence of VTE or study drug discontinuation due to death) showed that the two treatment groups were not significantly different (log-rank p = 0.65). The percentages of patients with treatment failure were 80/338 (24%) for the Fragmin group and 70/338 (21%) for the OAC group.

Of note, the rates of hospitalization during the six month treatment period were similar between the two study groups (see appendix). Conceptually, a robust treatment benefit related to a reduction in the risk for recurrent VTE might also be suggested by a reduction in hospitalizations.

<u>Inconsistencies in primary endpoint exploratory subsets, especially the non-metastatic cancer population:</u>

Post-hoc, exploratory primary endpoint subset analyses generally provide limited value due to multiplicity concerns. However, these explorations may provide useful insight in the situation where a single study is proposed to provide robust evidence of efficacy. Subset analyses of the CLOT study's primary endpoint did not consistently show superiority of Fragmin over OAC. Most notably, unfavorable Fragmin findings were suggested for patients with non-metastatic cancer as well as patients with hematological cancer, although these subgroups were generally very small (see appendix).

Safety findings:

Overall, the most notable safety findings were that, compared to the OAC group, more Fragmin patients discontinued the assigned study drug due to death and the patients on Fragmin experienced numerically higher rates of major bleeding, thrombocytopenia, and elevation of hepatic enzymes.

Discontinuation of Fragmin due to death:

As previously noted, twice as many patients discontinued Fragmin (17%) due to death as compared to patients receiving OAC (7%). This imbalance may relate to informative censoring due to the differing anticoagulant management between the study groups. For example, physicians may have been inclined to more readily discontinue OAC than the injectable Fragmin drug. Notably, Fragmin patients remained on treatment slightly longer than OAC patients as indicated by the median duration of treatment for Fragmin-treated patients relative to patients treated with OAC (176 days vs 167 days, respectively).

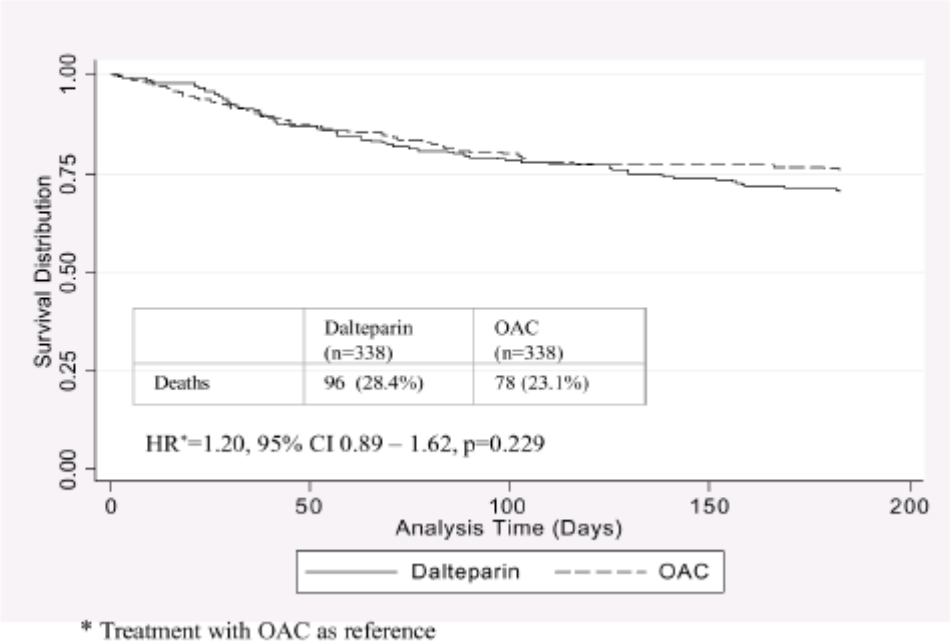
The sponsor supplied the following table to illustrate the death rate by month among the patients receiving the assigned study treatments (the "on treatment" population). This table includes a post-study six month follow-up period (ie., the randomized assigned treatment portion of the study was limited to the first six months). As noted in the table, the "crude death rates" were generally numerically higher for the Fragmin group throughout the controlled, six month study treatment period.

Table 4. Crude Death Rates among "On Treatment" Patients, by Month,

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

As will be subsequently shown, the overall mortality rates were similar between patients in the two study arms. To support the contention that varying study agent management between the study groups explained the imbalance in study drug discontinuation due to death, the sponsor notes that when "on treatment" death rates are compared using a 14 day time window (i.e., deaths within 14 days after study agent discontinuation), the death rates are similar between the study groups. This observation is illustrated by the following survival curve:

Figure 3. On-Treatment Survival Distribution During Six-Month Treatment Period By Treatment Observations Censored 14 Days Post-Treatment Withdrawal ITT Population



* Treatment with OAC as reference

FDA Review Team Comments: Deaths related to hemorrhage or other suspected Fragmin-related effects do not account for the imbalance in study drug discontinuations due to death. In general, a difference in patient management between the two study groups is a plausible explanation for the imbalance However, variance in patient management raises questions regarding other outcomes that may have also been influenced by variations in patient management, such as the occurrence and detection of VTE symptoms. For example, the intensity of INR monitoring in the OAC group may have coincidentally resulted in more intense monitoring for VTE symptoms.

Major bleeding:

The number of patients with at least one major bleeding event was numerically higher in the Fragmin arm (5.6%) than in the OAC arm (3.6%). The majority of major bleeding episodes in the Fragmin arm occurred in the first month (13 of 22 episodes) when the higher dose of Fragmin was administered. The following table summarizes the major bleeding events by time of occurrence.

Table 5. Timing of Adjudicated Major Bleeding Events (As treated population)[1]

Study Period	Fragmin		OAC	
	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.

Only one patient suffered a fatal bleeding event while receiving a study agent. As noted below, a Fragmin-treated patient with lung cancer experienced fatal hemoptysis.

A numerically higher frequency of any bleeding was observed in the OAC arm (18.5%) than in the Fragmin arm (13.6%).

Thrombocytopenia:

Thrombocytopenia was reported as a treatment emergent adverse event in 37 (11%) of patients in the Fragmin arm and 27 (8.2%) of patients in the OAC arm. Table 6 shows the study results for the occurrence of severe thrombocytopenia when "severe thrombocytopenia" is defined as the presence of any platelet count < 50,000/mcL.

Table 6. Severe Thrombocytopenia (≤ 50,000/mcL) by Treatment Week

Study month	Fragmin		OAC	
	n	Patients with Severe T'penia	n	Patients with Severe T'penia
< 1 month	338	11 (3.3%)	338	5 (1.5%)
1 to < 6 months	302	10 (3.3%)	301	4 (1.3%)

Study drug modification or interruption due to decreased platelet counts was reported in 27 Fragmin patients and five OAC patients. Thrombocytopenia was the basis for study agent discontinuation in five Fragmin® patients and one OAC patient.

Two cases of antibody positive, heparin induced thrombocytopenia were reported among Fragmin patients. As noted in the current Fragmin label, heparin-induced thrombocytopenia can occur with Fragmin administration.

Hepatic transaminases:

Liver enzyme elevations (ALT, AST, GGT) were noted among more Fragmin patients when compared to OAC (39.9% vs. 31.0%, 34.3% vs. 28.4%, 41.1% vs. 31.3% of patients respectively).

The following table summarizes the numbers of patients with treatment-emergent abnormal elevation of liver enzymes by Common Toxicity Criteria (CTC) severity grade.

Table 7. Patients with Treatment-emergent Elevations of Liver Enzymes or Bilirubin

Laboratory Parameter	Dalteparin N=338				OAC N=336			
	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
γ-GT	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

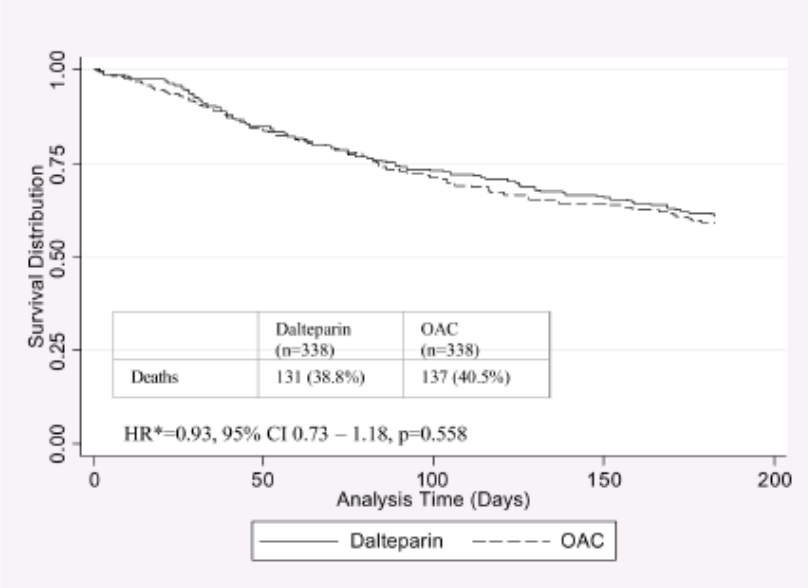
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; γ-GT = gamma-glutamyl transpeptidase; OAC = oral anticoagulant

In contrast to the numerical disproportion in liver enzyme findings, only one Fragmin patient and two OAC patients discontinued the assigned study agent due to hepato-biliary disease.

Deaths:

As previously noted, more Fragmin patients discontinued the assigned study treatment due to death than OAC patients. The overall (randomized population) survival curve is shown below.

Figure 1. Survival Distribution During Six-Month Treatment Period By Treatment ITT Population



* Treatment with OAC as reference

By the six month follow-up time point, 131/338 (39%) Fragmin patients and 137/338 (41%) OAC patients died. The majority of deaths were assessed as due to disease progression (90.8% in the Fragmin arm vs. 90.5% in the OAC arm).

The frequency of death due to non-cancer related causes was similar between the two treatment arms (3.6% [12/338] in the Fragmin arm vs. 3.9% [13/335] in the OAC arm).

Fatal bleeding was the cause of death in three patients in the Fragmin group and one in the OAC group. Of the three patients in the Fragmin group, one death from hemoptysis occurred during treatment in a lung cancer patient, while the other two deaths occurred after treatment discontinuation (one patient died of cerebellar hemorrhage 20 days after treatment discontinuation and one patient 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) five days after treatment discontinuation.

Appendix: Clot Summary Tables

Tables supplementing the Executive Summary text.

Table 8. Baseline Characteristics

Characteristic	Fragmin n = 338	OAC n = 338
Age Distribution		
< 65	182 (53.8%)	182 (53.8%)
≥ 65	156 (46.2%)	156 (46.2%)
Gender		
Male	159 (47.0%)	169 (50.0%)
Female	179 (53.0%)	169 (50.0%)
Performance Status/ECOG		
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%)
GI	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%)
Solid Tumor Status		
No evidence of tumor	36 (12.1%)	33 (10.7%)
Localized/no metastases	39 (13.1%)	43 (14.0%)
Metastatic	223 (74.8%)	232 (75.3%)
Tumor Treatment (last 6 wks)		
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%)

Table 9. Post-hoc, Exploratory Subset Analyses of the Primary Endpoint of First Recurrent VTE

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%)
Hematol	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%)
GI	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-U	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%)
Hematol	4/40 (10.0%)	0/30 (0.0%)	10.0%	(0.7%, 19.3%)
Extent of Tumor				
Non Meta	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%)

Table 10. Study Agent Discontinuation due to Death, by Countries

Country	Fragmin	OAC	Diff	95% C.I.
Canada	23/126 (18.3%)	9/129 (7.0%)	11.3%	(3.2%, 19.3%)
U.S.	5/58 (8.6%)	2/60 (3.3%)	5.3%	(-3.2%, 13.8%)
Italy	10/34 (29.4%)	4/33 (12.1%)	17.3%	(-1.6%, 36.2%)
Australia	6/73 (8.2%)	3/71 (4.2%)	4.0%	(-3.9%, 11.8%)
New Zealand	1/8 (12.5%)	0/8 (0.0%)	12.5%	(-10.4%, 35.4%)
The Netherlands	6/22 (27.3%)	4/19 (21.0)	6.3%	(-19.9%, 32.3%)
Spain	5/16 (31.3%)	2/17 (11.8%)	19.5%	(-7.9%, 46.9%)

Table 11. Summary of Hospitalizations

Patients with at least one hospitalization	Fragmin n = 338	OAC n = 335
1 hospitalization	104 (30.8%)	94 (28.1%)
2 hospitalizations	70 (20.7%)	63 (18.8%)
> 2 hospitalizations	10 (3.0%)	15 (4.5%)

Topics for Committee Questions

FDA anticipates posing questions relating to the following major topics:

1. The extent to which variation in patient anticoagulation management may have impacted the CLOT study findings.

2. The consequences of the competing risks of death and recurrent VTE upon the CLOT study primary endpoint results.

3. The CLOT study safety findings, especially with respect to the occurrence of major hemorrhage and the reasons for study drug discontinuation during the treatment period.

4. Implications of the CLOT study findings for Fragmin use among patients without cancer.

5. Assessment of the robustness of the CLOT study's primary endpoint result.

6. The need for any additional clinical studies to more definitively assess the use of Fragmin in the treatment of VTE.

7. Considerations of the "extended" use of Fragmin for the treatment of VTE among cancer patients.

Fragmin®

dalteparin sodium injection

PHARMACIA

For *Subcutaneous* Use Only

SPINAL/EPIDURAL HEMATOMAS

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

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

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

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

DESCRIPTION

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

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

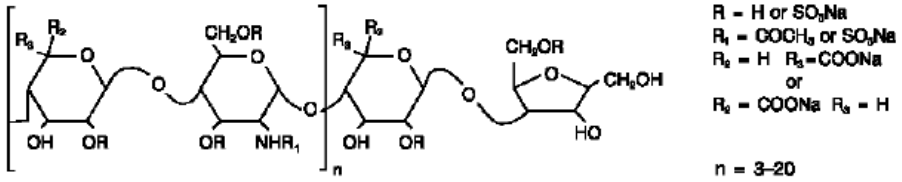
Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulphated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues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

<3000 daltons	3.0-15%
3000 to 8000 daltons	65.0-78.0%
>8000 daltons	14.0-26.0%

Fragmin

brand of dalteparin sodium injection

Structural Formula



CLINICAL PHARMACOLOGY

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

Pharmacodynamics:

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

Pharmacokinetics:

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

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

The volume of distribution for dalteparin anti-Factor Xa activity was 40 to 60 mL/kg. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single intravenous bolus doses of 30 and 120 anti-Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 mL/hr/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 and 2.5 ± 0.3 hours.

Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer apparent terminal half-lives (3 to 5 hours) are observed following s.c. dosing, possibly due to delayed absorption. In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Factor Xa activity following a single intravenous dose of 5000 IU FRAGMIN was 5.7 ±

2.0 hours, i.e. considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

CLINICAL TRIALS

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

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

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

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

[1] p-value = 0.001

In a second randomized, controlled trial designed to evaluate long-term treatment with FRAGMIN (days 6 to 45), data were also collected comparing 1-week (5 to 8 days) treatment of FRAGMIN 120 IU/kg every 12 hours s.c. with heparin at an APTT-adjusted dosage. All patients, except when contraindicated, were treated concurrently with aspirin (100 to 165 mg per day). Of the total enrolled study population of 1499 patients, 1482 patients were treated; 751 received FRAGMIN and 731 received heparin. The mean age of the study population was 64 years (range 25 to 92 years) and the majority of patients were white (96.0%) and male (64.2%). The incidence of the combined triple endpoint of death, myocardial infarction, or recurrent angina during this 1-week treatment period (5 to 8 days) was 9.3% for FRAGMIN and 7.6% for heparin (p=0.323).

Prophylaxis of Deep Vein Thrombosis in Patients Following Hip Replacement Surgery:
In an open-label randomized study, FRAGMIN 5000 IU administered once daily s.c. was compared with warfarin sodium, administered orally, in patients undergoing hip replacement surgery. Treatment with FRAGMIN was initiated with a 2500 IU dose s.c. within 2 hours before surgery, followed by a 2500 IU dose s.c. the evening of the day of surgery. Then, a dosing regimen of FRAGMIN 5000 IU s.c. once daily was initiated on the first postoperative day. The first dose of warfarin sodium was given the evening before surgery, then continued daily at a dose adjusted for INR 2.0 to 3.0. Treatment in both groups was then continued for 5 to 9 days postoperatively. Of the total enrolled study population of 580 patients, 553 were treated and 550 underwent surgery. Of those who underwent surgery, 271 received FRAGMIN and 279 received warfarin sodium. The mean age of the study population was 63 years (range 20 to 92 years) and the majority of patients were white (91.1%) and female (52.9%). The incidence of deep vein thrombosis (DVT), any vein, as determined by evaluable venography, was significantly lower for the group treated with FRAGMIN compared with patients treated with warfarin sodium (28/192 vs 49/190; p=0.006) [see Table 2].

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

Indication	Dosing Regimen	
	FRAGMIN 5000 IU qd[1] s.c.	Warfarin Sodium qd[2] oral
All Treated Hip Replacement Surgery Patients	271	279
Treatment Failures in Evaluable Patients		
DVT, Total	28/192 (14.6%)[3]	49/190 (25.8%)
Proximal DVT	10/192 (5.2%)[4]	16/190 (8.4%)
PE	2/271 (0.7%)	2/279 (0.7%)

[1] The daily dose on the day of surgery was divided: 2500 IU was given two hours before surgery and again in the evening of the day of surgery.
[2] Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
[3] p-value = 0.006
[4] p-value = 0.185

In a second single-center, double-blind study of patients undergoing hip replacement surgery, FRAGMIN 5000 IU once daily s.c. starting the evening before surgery, was compared with heparin 5000 U s.c. tid, starting the morning of surgery. Treatment in both groups was continued for up to 9 days postoperatively. Of the total enrolled study population of 140 patients, 139 were treated and 136 underwent surgery. Of those who underwent surgery, 67 received FRAGMIN and 69 received heparin. The mean age of the study population was 69 years (range 42 to 87 years) and the majority of patients were female (58.8%). In the intent-to-treat analysis, the incidence of proximal DVT was significantly lower for patients treated with FRAGMIN compared with patients treated with heparin (6/67 vs 18/69; p=0.012). Further, the incidence of pulmonary embolism detected by lung scan was also significantly lower in the group treated with FRAGMIN (9/67 vs 19/69; p=0.032).

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

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

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

Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications:

Abdominal surgery patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes, or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism.

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

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

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	**Placebo** qd s.c.
All Treated Abdominal Surgery Patients	102	102
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	4/91 (4.4%)[1]	16/91 (17.6%)
Proximal DVT	0	5/91 (5.5%)
Distal DVT	4/91 (4.4%)	11/91 (12.1%)
PE	0	2/91 (2.2%)[2]

[1] p-value = 0.008
[2] Both patients also had DVT , 1 proximal and 1 distal

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

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	Heparin 5000 U bid s.c.
All Treated Abdominal Surgery Patients	195	196
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	7/178 (3.9%)[1]	7/174 (4.0%)
Proximal DVT	3/178 (1.7%)	4/174 (2.3%)
Distal DVT	3/178 (1.7%)	3/174 (1.7%)
PE	1/178 (0.6%)	0

[1] p-value = 0.74

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

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

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	FRAGMIN 5000 IU qd s.c.
All Treated Abdominal Surgery Patients[1]	696	679
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	99/656 (15.1%)[2]	60/645 (9.3%)
Proximal DVT	18/657 (2.7%)	14/646 (2.2%)
Distal DVT	80/657 (12.2%)	41/646 (6.3%)
PE		
Fatal	1/674 (0.1%)	1/669 (0.1%)
Non-fatal	2	4

[1] Major abdominal surgery with malignancy
[2] p-value = 0.001

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

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

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

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

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

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

[2] p-value = 0.0015

INDICATIONS AND USAGE
FRAGMIN Injection is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy (as described in CLINICAL TRIALS, Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction).
FRAGMIN is also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

CONTRAINDICATIONS
FRAGMIN Injection is contraindicated in patients with known hypersensitivity to the drug, active major bleeding, or thrombocytopenia associated with positive *in vitro* tests for anti-platelet antibody in the presence of FRAGMIN.
Patients undergoing regional anesthesia should not receive FRAGMIN for unstable angina or non-Q-wave myocardial infarction due to an increased risk of bleeding associated with the dosage of FRAGMIN recommended for unstable angina and non-Q-wave myocardial infarction.
Patients with known hypersensitivity to heparin or pork products should not be treated with FRAGMIN.

WARNINGS
FRAGMIN Injection is not intended for intramuscular administration.
FRAGMIN cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins.
FRAGMIN should be used with extreme caution in patients with history of heparin-induced thrombocytopenia.

Hemorrhage:
FRAGMIN, like other anticoagulants, should be used with extreme caution in patients who have an increased risk of hemorrhage, such as those with severe uncontrolled hypertension, bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal or ophthalmological surgery.
Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and neuraxial (spinal/epidural) anesthesia or spinal puncture, which can result in long-term or permanent paralysis. The risk of these events is higher with the use of indwelling epidural catheters or concomitant use of

additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING and ADVERSE REACTIONS, Ongoing Safety Surveillance).
As with other anticoagulants, bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia:
In clinical trials, thrombocytopenia with platelet counts of < 100,000/mm^3 and < 50,000/mm^3 occurred in < 1% and < 1%, respectively. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed.
Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. The incidence of this complication is unknown at present.
Miscellaneous:
The multiple-dose vial of FRAGMIN contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see PRECAUTIONS, Pregnancy Category B, Nonteratogenic Effects).

PRECAUTIONS
General:
FRAGMIN Injection should not be mixed with other injections or infusions unless specific compatibility data are available that support such mixing.
FRAGMIN should be used with caution in patients with bleeding diathesis, thrombocytopenia or platelet defects; severe liver or kidney insufficiency, hypertensive or diabetic retinopathy, and recent gastrointestinal bleeding.
If a thromboembolic event should occur despite dalteparin prophylaxis, FRAGMIN should be discontinued and appropriate therapy initiated.

Drug Interactions:
FRAGMIN should be used with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding (see **PRECAUTIONS, Laboratory Tests**). Aspirin, unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarction (see **DOSAGE AND ADMINISTRATION**).

Laboratory Tests:
Periodic routine complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with FRAGMIN. No special monitoring of blood clotting times (e.g., APTT) is needed.
When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are

relatively insensitive measures of FRAGMIN activity and, therefore, unsuitable for monitoring.

Drug/Laboratory Test Interactions:
Elevations of Serum Transaminases:
Asymptomatic increases in transaminase levels (SGOT/AST and SGPT/ALT) greater than three times the upper limit of normal of the laboratory reference range have been reported in 1.7 and 4.3%, respectively, of patients during treatment with FRAGMIN. Similar significant increases in transaminase levels have also been observed in patients treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since transaminase determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary emboli, elevations that might be caused by drugs like FRAGMIN should be interpreted with caution.

Carcinogenicity, Mutagenesis, Impairment of Fertility:
Dalteparin sodium has not been tested for its carcinogenic potential in long-term animal studies. It was not mutagenic in the *in vitro* Ames Test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and in the *in vivo* mouse micronucleus test. Dalteparin sodium at subcutaneous doses up to 1200 IU/kg (7080 IU/m^2) did not affect the fertility or reproductive performance of male and female rats.

Pregnancy: Pregnancy Category B.
Teratogenic Effects:
Reproduction studies with dalteparin sodium at intravenous doses up to 2400 IU/kg (14,160 IU/m^2) in pregnant rats and 4800 IU/kg (40,800 IU/m^2) in pregnant rabbits did not produce any evidence of impaired fertility or harm to the fetuses. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

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

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

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

ADVERSE REACTIONS
Hemorrhage:
The incidence of hemorrhagic complications during treatment with FRAGMIN Injection has been low. The most commonly reported side effect is hematoma at the injection site. The incidence of bleeding may increase with higher doses; however, in abdominal surgery patients with malignancy, no significant increase in bleeding was observed when comparing FRAGMIN 5000 IU to either FRAGMIN 2500 IU or low dose heparin.
In a trial comparing FRAGMIN 5000 IU once daily to FRAGMIN 2500 IU once daily in patients undergoing surgery for malignancy, the incidence of bleeding events was 4.6% and 3.6%, respectively (n.s.). In a trial comparing FRAGMIN 5000 IU once daily to heparin 5000 U twice daily, the incidence of bleeding events was 3.2% and 2.7%, respectively (n.s.) in the malignancy subgroup.
Unstable Angina and Non-Q-Wave Myocardial Infarction:
Table 7 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

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

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

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

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

Table 8
Bleeding Events Following Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	FRAGMIN 5000 IU qd s.c. (n=274[2])	Warfarin Sodium[1] oral (n=279)	FRAGMIN 5000 IU qd s.c. (n=69[4])	Heparin 5000 U tid s.c. (n=69)
Major Bleeding Events[3]	7/274 (2.6%)	1/279 (0.4%)	0	3/69 (4.3%)
Other Bleeding Events[5]				
Hematuria	8/274 (2.9%)	5/279 (1.8%)	0	0
Wound Hematoma	6/274 (2.2%)	0	0	0
Injection Site Hematoma	3/274 (1.1%)	NA	2/69 (2.9%)	7/69 (10.1%)

[1] Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
[2] Includes three treated patients who did not undergo a surgical procedure.
[3] A bleeding event was considered major if: 1) hemorrhage caused a significant clinical event, 2) it was associated with a hemoglobin decrease of ≥ 2 g/dL or transfusion of 2 or more units of blood products, 3) it resulted in reoperation due to bleeding, or 4) it involved retroperitoneal or intracranial hemorrhage.

[4] Includes two treated patients who did not undergo a surgical procedure.
[5] Occurred at a rate of at least 2% in the group treated with FRAGMIN 5000 IU once daily.

Six of the patients treated with FRAGMIN experienced seven major bleeding events. Two of the events were wound hematoma (one requiring reoperation), three were bleeding from the operative site, one was intraoperative bleeding due to vessel damage, and one was gastrointestinal bleeding. None of the patients experienced retroperitoneal or intracranial hemorrhage nor died of bleeding complications.
In the third hip replacement surgery clinical trial, the incidence of major bleeding events was similar in all three treatment groups: 3.6% (18/496) for patients who started FRAGMIN before surgery; 2.5% (12/487) for patients who started FRAGMIN after surgery; and 3.1% (15/489) for patients treated with warfarin sodium.

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

Table 9
Bleeding Events Following Abdominal Surgery

Indication	FRAGMIN vs Heparin				FRAGMIN vs Placebo		FRAGMIN vs FRAGMIN	
	Dosing Regimen				Dosing Regimen		Dosing Regimen	
Abdominal Surgery	**FRAGMIN** 2500 IU qd s.c.	**Heparin** 5000 U bid s.c.	**FRAGMIN** 5000 IU qd s.c.	**Heparin** 5000 U bid s.c.	**FRAGMIN** 2500 IU qd s.c.	**Placebo** qd s.c.	**FRAGMIN** 2500 IU qd s.c.	**FRAGMIN** 5000 IU qd s.c.
Postoperative	26/459	36/454	81/508	63/498	14/182	13/182	89/1025	125/1033
Transfusions	(5.7%)	(7.9%)	(15.9%)	(12.7%)	(7.7%)	(7.1%)	(8.7%)	(12.1%)
Wound	16/467	18/467	12/508	6/498	2/79	2/77	1/1030	4/1039
Hematoma	(3.4%)	(3.9%)	(2.4%)	(1.2%)	(2.5%)	(2.6%)	(0.1%)	(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 10 summarizes major bleeding events that occurred in a clinical trial of medical patients with severely restricted mobility during acute illness.

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

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

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

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

Thrombocytopenia: **See WARNINGS: Thrombocytopenia.**

Other:
Allergic Reactions:
Allergic reactions (i.e., pruritus, rash, fever, injection site reaction, bulleous eruption) and skin necrosis have occurred rarely. A few cases of anaphylactoid reactions have been reported.

Local Reactions:
Pain at the injection site, the only non-bleeding event determined to be possibly or probably related to treatment with FRAGMIN and reported at a rate of at least 2% in the group treated with FRAGMIN, was reported in 4.5% of patients treated with FRAGMIN 5000 IU qd vs 11.8% of patients treated with heparin 5000 U bid in the abdominal surgery trials. In the hip replacement trials, pain at injection site was reported in 12% of patients treated with FRAGMIN 5000 IU qd vs 13% of patients treated with heparin 5000 U tid.
Ongoing Safety Surveillance:
Since first international market introduction in 1985, there have been nine reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. Five of the nine patients had post-operative indwelling epidural catheters placed for analgesia or received additional drugs affecting

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

OVERDOSAGE

Symptoms/Treatment:

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

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

DOSAGE AND ADMINISTRATION

Unstable Angina and Non-Q-Wave Myocardial Infarction:

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

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

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

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

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

Table 12
Dosing Options for Patients Undergoing Hip Replacement Surgery

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

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

Fragmin

brand of dalteparin sodium injection

Abdominal Surgery:
In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of FRAGMIN is 2500 IU administered by s.c. injection once daily, starting 1 to 2 hours prior to surgery and repeated once daily postoperatively. The usual duration of administration is 5 to 10 days.
In patients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignant disorder, the recommended dose of FRAGMIN is 5000 IU s.c. the evening before surgery, then once daily postoperatively. The usual duration of administration is 5 to 10 days. Alternatively, in patients with malignancy, 2500 IU of FRAGMIN can be administered s.c. 1 to 2 hours before surgery followed by 2500 IU s.c. 12 hours later, and then 5000 IU once daily postoperatively. The usual duration of administration is 5 to 10 days.
Dosage adjustment and routine monitoring of coagulation parameters are not required if the dosage and administration recommendations specified above are followed.

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

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

Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep s.c. injection. FRAGMIN may be injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. The injection site should be varied daily. When the area around the navel or the thigh is used, using the thumb and forefinger, you **must** lift up a fold of skin while giving the injection. The entire length of the needle should be inserted at a 45 to 90 degree angle.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to 2 weeks. Discard any unused solution after 2 weeks.

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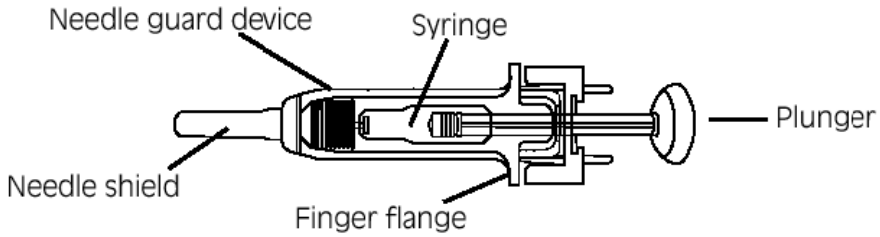
Instructions for using the prefilled single-dose syringes preassembled with needle guard devices:



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

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

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

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

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

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

Fragmin
brand of dalteparin sodium injection

Package of 10:
7500 anti-Factor Xa IU NDC 0013-2426-01

1.0 mL single-dose graduated syringe, affixed with a 27-gauge x 1/2 inch needle and preassembled with UltraSafe Passive™ Needle Guard* devices.
Package of 10:
10,000 anti-Factor Xa IU NDC 0013-5190-01

3.8 mL multiple-dose vial:
25,000 anti-Factor Xa IU/mL 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].

℞ only

U.S. Patent 4,303,651
* UltraSafe Passive™ Needle Guard is a trademark of Safety Syringes, Inc.

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

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

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

818 312 112 Revised March 2004