



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dalteparin

Proprietary Product Name: Fragmin

Sponsor: Pfizer Australia Pty Ltd

May 2010

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Product Details

<i>Type of Submission</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	1 April 2010
<i>Active ingredient(s):</i>	Dalteparin
<i>Product Name(s):</i>	Fragmin
<i>Sponsor's Name and Address:</i>	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
<i>Dose form(s):</i>	Solution for injection
<i>Strength(s):</i>	2,500 AntiXa IU/0.2 mL, 5,000 AntiXa IU/0.2 mL, 7,500 AntiXa IU/0.75 mL, 10,000 AntiXa IU/1 mL, 12,500 AntiXa IU/0.5 mL, 15,000 AntiXa IU/0.6 mL and 18,000 AntiXa IU/0.72 mL
<i>Container(s):</i>	Single dose syringe: 0.2 mL, 0.5 mL, 0.6 mL, 0.72 mL. Graduated single dose syringe: 0.75 mL, 1 mL
<i>Pack size(s):</i>	Single dose syringe: 0.2 mL: 10's; 0.5 mL, 0.6 mL, 0.72 mL: 5's. Graduated single dose syringe: 10's
<i>Approved Therapeutic use:</i>	Prophylaxis against thrombotic complications during haemodialysis and treatment of acute deep vein thrombosis (DVT). Extended treatment of symptomatic venous thromboembolism (VTE) (proximal deep vein thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with solid tumour cancers. Treatment of unstable coronary artery disease, i.e. unstable angina and non-ST-elevation myocardial infarction (also known as non-Q-wave myocardial infarction). Prophylaxis against thrombo-embolic complications in the peri- or postoperative period of surgery.
<i>Route(s) of administration:</i>	Subcutaneous, intravenous - varies with indication
<i>Dosage:</i>	Varies with indication
<i>ARTG Numbers:</i>	25347, 25349, 61937, 61938, 61939, 66625, 66626

Product Background

Fragmin (dalteparin) is a low molecular weight heparin that acts by accelerating the rate of the neutralisation of certain activated coagulation factors, largely Factor Xa, but also Factor XIIa and kallikrein by antithrombin.

The submission by Pfizer Australia Pty Ltd sought to extend the indications for Fragmin to reduce the recurrence of VTE in cancer patients with VTE and to also add clinical trial

information to the PI from previously approved indications. This AusPAR only concerns the extension of indications.

Currently Fragmin has the following indications:

Prophylaxis against thrombotic complications during haemodialysis and treatment of acute deep venous thrombosis

Treatment of unstable coronary artery disease, i.e. unstable angina and non-Q-wave myocardial infarction

Prophylaxis against thromboembolic complications in the peri or postoperative period of surgery

The proposed new indication is:

Extended treatment of symptomatic venous thromboembolism [VTE] (proximal vein thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with cancer

Regulatory Status

A similar application to the current Australian submission had been approved in Canada (7 October 2004) and the US (1 May 2007). A similar application has also been approved in Austria, Belgium, Bulgaria, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Latvia, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom. A similar application has been submitted, and is undergoing review, in Germany. A similar application has been rejected in Italy and Switzerland.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in an application of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in an application of this type.

IV. Clinical Findings

Introduction

The submission included data from one pivotal study, one supportive study and four post-marketing reports.

The pivotal study is: *Study 98-FRAG-069* (Table 1), conducted in 667 subjects, 338 of whom were treated with dalteparin.

The supportive study is: *Study 98-FRAG-076* (Table 3) conducted in 439 subjects, 285 of whom were treated with dalteparin.

The post-marketing reports were:

- Periodic Safety Update Reports 1 December 1999 to 30 November 2004
- Addendum To The Periodic Safety Update Report 1 December 2004 to 30 June 2007

- Summary Bridging Report 1 December 1999 to 31 August 2006

The studies were stated to have been conducted according to Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki.

Pharmacokinetics

No new pharmacokinetic data were included in the submission.

Pharmacodynamics

No new pharmacodynamic data were included in the submission.

Efficacy

Pivotal Study

Study 98-FRAG-069 was a multinational, multicentre, Phase III, randomised, open-label, comparator controlled, parallel group clinical trial in cancer patients with acute symptomatic proximal lower limb deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (Table 1). The study was sponsored by Pharmacia Italia Spa and conducted at 48 centers: 14 in the US, eleven in Australia, ten in Canada, six in the Netherlands, three in Italy, two in England, and one each in New Zealand and Spain.

The study included hospitalized patients or outpatients with a malignancy as described in Table 1 and with an objectively documented acute symptomatic proximal lower limb DVT, defined as the presence of thrombus in the popliteal or more proximal vein; or PE; or both

The exclusion criteria included:

- Body weight ≤ 40 kg
- Recurrent spontaneous fractures unrelated to the underlying active malignancy
- Administration of therapeutic doses of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for more than 48 hours prior to randomization
- Need for long-term oral anticoagulant therapy other than for VTE prevention (for example, mechanical heart valves or atrial fibrillation)
- Poor performance status with a score of 3 or 4 according to the Eastern Cooperative Oncology Group (ECOG) scale
- Serious haemorrhage requiring hospitalisation, transfusion, or surgical intervention within 2 weeks of presentation
- Known acute (symptomatic or actively bleeding) gastroduodenal ulcer
- Epidural/spinal puncture within the last 24 hours
- Neurosurgery within 4 weeks of presentation or any previous history of intracranial haemorrhage
- Septic endocarditis
- Overt pericardial effusion
- Baseline platelet count of $<75 \times 10^9/L$
- Undergoing high-dose chemotherapy with peripheral blood stem cell or bone marrow transplantation, induction chemotherapy for acute leukaemia, or have other conditions associated with persistent thrombocytopenia of $<100 \times 10^9/L$ for a duration of ≥ 4 consecutive weeks
- Familial bleeding diathesis
- Uncontrolled hypertension despite antihypertensive therapy
- Dependent on renal dialysis or significant renal failure with a creatinine >3 x the upper limit of normal (ULN)

- Allergy to anticoagulants (UFH, LMWH, or coumarin derivatives) including immune-mediated heparin-induced thrombocytopenia
- Allergy to contrast medium
- Pregnant or of childbearing potential and not using adequate contraception

Table 1: Details of Study 98-FRAG-069

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Test Product Dosage Regimen Route of administration , Formulation Duration	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
677 subjects were randomized to treatment: 338 to dalteparin and 339 to OAC. Data from 338 patients in each group were included in the ITT data set. There were 328 (48.5%) males and 348 (51.5%) females. age range was 22 to 89 years.	<p>Hospitalized patients or outpatients ≥ 16 years of age with DVT and:</p> <p>Presence of a documented active malignancy, excluding basal cell or squamous cell carcinoma of the skin. The criteria for active malignancy were:</p> <p>a. Diagnosis of cancer within 6 months prior to randomization; or</p> <p>b. Past administration of treatment (surgery, radiation, chemotherapy, hormonal therapy, palliative, or combined modality therapy) for cancer within 6 months prior to randomization; or</p> <p>c. Ongoing administration of treatment (surgery, radiation, chemotherapy, hormonal therapy, palliative, or combined modality therapy) for cancer at randomization; or</p> <p>d. Documentation of recurrent or metastatic disease.</p>	<p>Month 1: dalteparin was administered SC once daily, at a dose of 200 IU/kg SC once daily with a maximum allowable total daily dose of 18,000 IU</p> <p>Month 2-6: dalteparin was administered SC once daily, at a dose of approximately 150 IU/kg (pre-filled syringes were supplied according to the patient's weight).</p> <p>Randomisation was centralised and stratified by study centre. Patients were randomly assigned in a 1:1 ratio to receive dalteparin or control therapy at the time of confirmed VTE diagnosis.</p> <p>6 months</p>	<p>Oral anticoagulation with a coumarin derivative</p> <p>From Day 1 to Day 5 and then until the INR was between 2.0-3.0 for 2 consecutive days: dalteparin was administered SC once daily, at a dose of 200 IU/kg</p> <p>Coumarin dose adjusted to a target 2.5 INR (range 2.0-3.0) from Day 1 through Month 6</p>	<p>The primary efficacy outcome measure was symptomatic, recurrent, lower limb DVT or PE or both occurring during the 6-month study period. The secondary efficacy outcome measures were the first occurrence of a symptomatic, and objectively documented lower limb DVT, or PE, or CVT; and death. Subjects enrolled in Canada also participated in a quality of life (QOL) measure. Hypothesis testing was performed using Kaplan Meier plots and the log-rank test.</p> <p>Safety outcome measures: bleeding events, AEs and laboratory tests</p>	<p>For the primary efficacy outcome measure, time to first event was greater in the dalteparin group, $p=0.0017$. A total of 27 (8.0%) subjects randomised to dalteparin and 53 (15.7%) randomised to OAC experienced DVT and/or PE during the 6-month study period. The cumulative probability (95% confidence intervals (CI)) of recurrence was 0.172 (0.129 to 0.215) in the OAC arm and 0.087 (0.055 to 0.119) in the dalteparin arm. The risk ratio of dalteparin to OAC was 0.48 (95% CI, 0.30-0.77). There was no significant difference between treatment groups in time to death.</p>	<p>283 (84.0%) subjects in the dalteparin group and 283 (85.5%) in the OAC reported at least one AE. The most frequently reported adverse events were nausea, vomiting, and fatigue. Study drug related AEs were reported in 121 (35.9%) subjects in the dalteparin group and 105 (31.7%) in the OAC. Major bleeding episodes were more common in the dalteparin group and one subject in the dalteparin group died due to a major bleeding episode. Ten (2.9%) subjects dalteparin group and five (1.5%) OAC discontinued treatment due to a major hemorrhagic event. Minor bleeding events were less common in the dalteparin group, 30 (8.9%) vs 50 (14.9%) OAC. Fifteen (4.4%) subjects in the dalteparin group and seven (2.1%) in the OAC were reported to have thrombocytopenia related to study medication. Death occurred at a similar rate for both treatment groups and was predominantly due to underlying cancer. SAEs were reported in 159 (47.2%) subjects in the dalteparin group and 147 (44.4%) in the OAC</p>

For the purpose of inclusion in the study, proximal lower limb DVT was defined as a clinically suspected diagnosis of proximal lower limb DVT confirmed by meeting one of the following criteria:

- A constant intraluminal filling defect in one or more views on contrast venography in one or more proximal venous segment (iliac, common femoral, superficial femoral, or popliteal vein).
- New or previously undocumented non-compressibility of one or more proximal venous segment on non-invasive compressive ultrasonography (CUS) (common femoral or popliteal vein).

For the purpose of inclusion in the study PE was defined as clinically suspected diagnosis of PE confirmed by meeting one of the following criteria:

- An intraluminal filling defect on a pulmonary angiogram.
- Sudden contrast cut-off of one or more vessels more than 2.5 mm in diameter on a pulmonary angiogram.
- A high probability ventilation perfusion (V/Q) lung scan showing one or more segmental perfusion defects with corresponding normal ventilation.
- An abnormal but non-high probability V/Q lung scan with satisfaction of the criteria for lower limb DVT.
- An unequivocal, intra-arterial, unenhancing filling defect in the central pulmonary vasculature (pulmonary trunk, right and left main pulmonary arteries, the anterior trunk, right and left interlobar and lobar arteries) on spiral CT scan.

The study treatments are described Table 1. Treatment duration was for 6 months. Both treatment arms were adjusted in the presence of thrombocytopenia. In the case of chemotherapy-induced thrombocytopenia with platelet counts $<50,000/\text{mm}^3$, both dalteparin and oral anticoagulant (OAC) were interrupted until the platelet count recovered above $50,000/\text{mm}^3$. For platelet counts between $50,000$ and $100,000/\text{mm}^3$, dalteparin was to be reduced by 17% to 33% of the initial dose depending on the patient's weight; and for OAC the target international normalised ratio (INR) was reduced to 2.0 with a range of 1.5-2.5. In the case of significant renal failure, defined as a creatinine level $>3 \times \text{ULN}$, the dose of dalteparin was adjusted to maintain an anti-Xa therapeutic level of 1 IU/mL (range 0.5-1.5 IU/mL) measured 4-6 hours after the dalteparin injection.

Outcome measures for Study 98-FRAG-069

The primary efficacy outcome measure was DVT or PE as described in Table 1. The secondary efficacy outcome measures as also described in Table 1 and include the first occurrence DVT, or PE, or central venous thrombosis of the upper limb(s), neck, or chest (CVT) during the 6-month study period; and death. The safety outcome measures were bleeding events (classified as major [defined as events that were clinically overt] or minor [defined as all the other overt hemorrhagic events]), adverse events (AEs) and clinical laboratory tests (haematology, coagulation and blood chemistry). The criteria for a major hemorrhagic event were:

- A decrease in haemoglobin of ≥ 20 g/L over a 24-hour period
- Bleeding leading to transfusion of ≥ 2 units of packed red cells
- Retroperineal, intracranial, intraspinal, intraocular, or pericardial bleeding documented by objective investigation
- Bleeding leading to death

Statistical analysis for Study 98-FRAG-069

The study was designed as a test of superiority with no provisions for a test of non-inferiority. Hypothesis testing was performed using Kaplan Meier plots and the log-rank test. A two-sided hypothesis test was performed with a level of significance of $p < 0.05$.

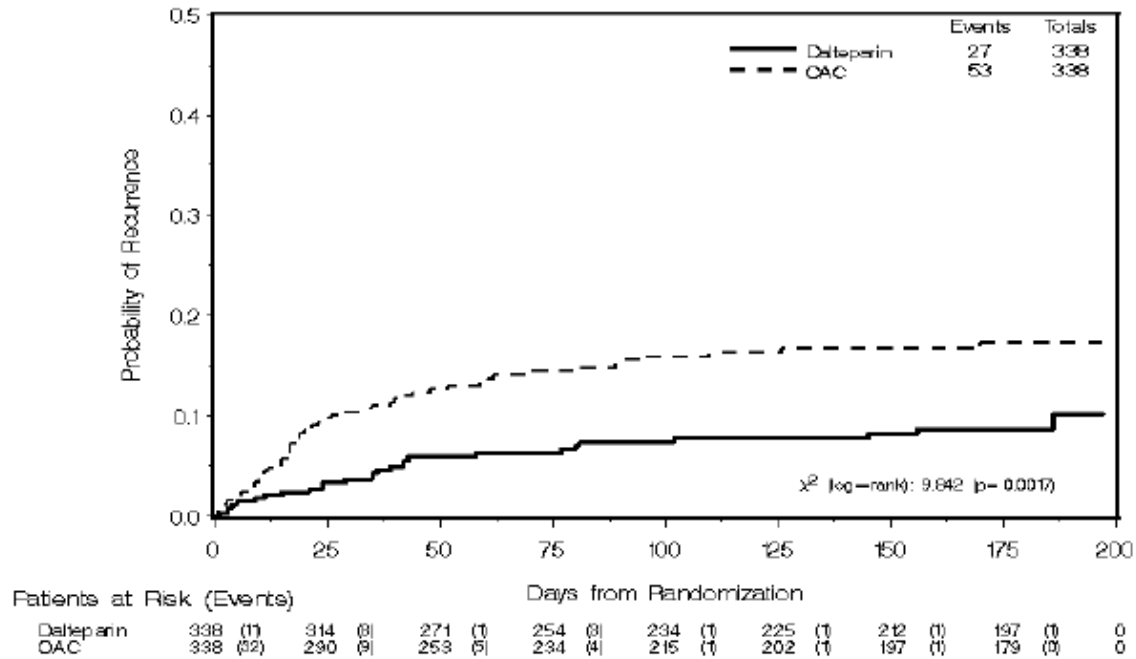
The sample size calculations used a historical incidence of 20% for recurrent VTE at 6 months in patients treated with OAC. Based on a Fisher's exact test, a sample size of 247 patients in each treatment group would be required to detect a 50% relative risk reduction in recurrent thromboembolism in the dalteparin group compared to the OAC group with a power of 0.85 and a two-sided alpha of 0.05.

Results for Study 98-FRAG-069

A total of 677 subjects were randomised to treatment: 338 to dalteparin and 339 to OAC. No data from one subject in the OAC group were collected. Hence data from 338 patients in each group were included in the intent-to-treat (ITT) data set. A total of 158 (46.7%) subjects in the dalteparin group and 172 (51.3%) in the OAC group discontinued study treatment. A greater number of subjects in the dalteparin group ceased treatment because of death due to cancer, and a greater number in the OAC group ceased because of VTE. There were 328 (48.5%) males and 348 (51.5%) females. The age range was 22 to 89 years. The treatment groups were similar in demographic characteristics, VTE characteristics at baseline and risk factors for VTE. The patients treated with 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. The OAC used was warfarin in 302 (89.3%) subjects and acenocoumarol in 36 (10.7%) subjects. Concomitant medications were received by 313 (92.6%) subjects in the dalteparin group and 316 (94.3%) in the OAC group. Concomitant medications with effects on coagulation were received by similar proportions of subjects in the two treatment groups. A slightly higher proportion of subjects in the OAC group were taking aspirin in addition to study treatment, but this would have been expected to bias the result in the favour of OAC. Anti-neoplastic therapy was administered to 75.1% of the dalteparin subjects and 69.6% of the OAC patients during the study.

For the primary efficacy outcome measure, time to first event was greater in the dalteparin group [logrank $p=0.0017$] (Figure 1). A total of 27 (8.0%) subjects randomised to dalteparin and 53 (15.7%) randomised to OAC experienced at least one adjudicated, symptomatic DVT and/or PE during the 6-month study period. The estimated cumulative probability (95% confidence intervals [CI]) of recurrence was 0.172 (0.129 to 0.215) in the OAC arm and 0.087 (0.055 to 0.119) in the dalteparin arm. There was a significant reduction of 52% in the risk of VTE recurrence over 6 months in the dalteparin arm, as the risk ratio of dalteparin to OAC was 0.48 (95% CI, 0.30-0.77); likelihood ratio test $p=0.0016$. The treatment effect for dalteparin remained when adjusted for covariates using a Cox proportional hazards model. The subgroup analysis indicated no benefit of dalteparin over OAC in patients with continuing VTE risk factors, and in the Netherlands and Spain (which were the countries where acenocoumarol rather than warfarin was used).

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



For the secondary efficacy outcome measures, the effect of dalteparin in decreasing risk of PE was less convincing than that for DVT (Table 2). The estimated probability (95% CI) for adjudicated DVT, PE, or CVT recurrence at 6 months was 0.095 (0.061 to 0.130) for dalteparin and 0.175 (0.132 to 0.218) for OAC (2-sided log-rank test, $p=0.0005$). There was no significant difference between treatment groups in time to death. There was no significant difference between treatments in the risk of death at 6 months: cumulative probability (95% CI) 0.39 (0.338 to 0.442) for dalteparin and 0.411 (0.358 to 0.464). There was no significant difference between treatments in the risk of death at 12 months: cumulative probability (95% CI) 0.561 (0.508 to 0.614) for dalteparin and 0.580 (0.527 to 0.634).

Table 2: 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

A total of 231 of 255 eligible subjects in the Canadian arm of the study participated in the quality of life (QOL) assessments: 116 dalteparin and 115 OAC. However, completion of the questionnaires was suboptimal with only approximately 40% of subjects completing all of the planned assessments. There was a significant benefit for dalteparin for social functioning [$p=0.024$]. However, there was more nausea and vomiting [$p=0.022$] and diarrhoea [$p=0.026$] with dalteparin relative to OAC. There was no significant difference between treatments for the other components of the quality of life assessment.

Evaluator's comments

Dalteparin was clearly superior to OAC for the primary efficacy outcome measure. However, the primary efficacy outcome measure might not be the most appropriate efficacy outcome measure. Although dalteparin decreased the risk of DVT or PE it did not alter the risk of death. However, if death had also been included in the outcome measure it might have been a more meaningful analysis. It is not clear from the study whether the disease burden for the subjects or health resource utilisation were altered by the treatment. The results of the quality of life measure were of limited utility because of the conflicting findings and suboptimal participation.

The high rates of discontinuation did not affect the ability to perform hypothesis testing because of the use of survival analysis.

The treatment effect was primarily for DVT rather than PE. However, both were included in the composite primary efficacy outcome measure, for which the study was powered. PE was a less common outcome in the study population and to have demonstrated a difference between the treatments, independently for the outcome of PE, would have required a much larger sample size. Hence it is reasonable to include both conditions in the indications.

With the exception of the primary efficacy outcome measure the Pivotal Study appears to have been conducted according to the European Medicines Agency Committee for Medicinal Products for Human Use (CPMP) guidance, adopted by the TGA.^{1,2} However, the results of the study are still open to interpretation with regard to the benefit to patients. There was no difference in the death rate between the treatment groups and the QOL analysis did not demonstrate any clear benefit for dalteparin. Hence the risk benefit profile is open to interpretation.

Supportive Study

Study 98-FRAG-076 was a multinational, multicentre, Phase III, randomized, double-blind, placebo-controlled, parallel group clinical trial in cancer patients who required placement of a central venous catheter (CVC) for administration of chemotherapy (Table 3). The study was sponsored by Pharmacia and conducted by 48 investigators in 12 countries: Austria, Canada, France, Germany, Greece, Portugal, Russian Federation, Slovak Republic, South Africa, Sweden, UK, and US).

The inclusion criteria are described in Table 3.

The exclusion criteria included:

- Subjects with known hypersensitivity (including heparin-induced thrombocytopenia) to dalteparin, heparin, or other LMWHs
- Subjects with active gastrointestinal or genitourinary tract bleeding
- Subjects with known coagulopathy
- Subjects requiring aspirin, dipyridamol, UFH, other LMWHs, warfarin or other anti-coagulation therapy (heparin flushing allowed)

¹ CPMP/EWP/563/98 Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease. Effective: 25 January 2001.

² CPMP/EWP/6235/04 Guideline on Clinical Investigation of Medicinal Products for the Prophylaxis of Venous Thromboembolic Risk in Non-Surgical Patients. Effective: 29 September 2006.

- Subjects with active uncontrolled infection, including suspected catheter-related infection, known human immunodeficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS)-related illness
- Subjects who within the past 3 months had undergone eye, ear, or central nervous system (CNS) surgery or who had experienced CNS trauma
- Subjects who had experienced an intracranial or intraocular haemorrhage (within 1 year) or retinal detachment (within 6 months)
- Subjects with uncontrolled hypertension, unstable angina, symptomatic congestive heart failure, myocardial infarction within the previous six months, or uncontrolled cardiac arrhythmia
- Subjects with other severe concurrent disease that, in the judgment of the investigator, would make the patient inappropriate for entry into this study
- Subjects with leukaemia who were to be undergoing induction/consolidation chemotherapy during the 16-week study period
- Subjects who were to be undergoing high-dose chemotherapy and stem cell transplantation during the 16-week study period
- Subjects who used investigational or unapproved catheter devices
- Pregnant or breastfeeding women or women of childbearing potential not practicing adequate birth control

The study treatments and treatment duration are described in Table 3. The placebo was normal saline.

Table 3: Details of Study 98-FRAG-076

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Test Product Dosage Regimen Route of administration, Formulation Duration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
439 subjects randomised patients: 294 to dalteparin, 145 to placebo 425 received study treatment: 285 received dalteparin, 140 received placebo 439 in the ITT population 425 in the As-treated population and analysed for safety 257 (58.5%) were female and 182 (41.5%) were male. Age range was 18 to 90 years.	Male and female patients aged ≥ 18 years (Austria was an exception: ≥ 19 years due to local laws) with a histopathologically documented malignancy and ECOG Performance Status of 0, 1, or 2, having undergone placement of a CVC for administration of chemotherapy within 5 days prior to randomization. The expected length of CVC use was to be ≥ 12 weeks. Patients must have had a predicted life expectancy of at least 16 weeks. There was no restriction on catheter type, unless it was investigational or unapproved.	Dalteparin 5000 IU (0.2 mL) was supplied as pre-filled, single-dose syringes for daily SC injection Patients were stratified by site of catheter insertion (proximal or distal to the axilla), and study site. Patients were randomly assigned in a 2:1 ratio to receive dalteparin or placebo Both study treatments were self-administered subcutaneously 16 weeks	The primary efficacy outcome measure was: catheter related complication consisting of a clinically relevant catheter related thrombosis (CRT); a clinically relevant catheter-related PE; or a catheter-related obstruction that required catheter removal. Secondary efficacy measures: asymptomatic CRT, catheter-related infection (CRI), clinically relevant non-catheter-related venous or arterial TEE. Safety outcome: AEs, haemorrhagic events.	For the primary efficacy outcome measure, there was a similar incidence of events in both treatment groups: 11 events (3.7%) in the dalteparin group and 5 (3.4%) in the placebo (p=0.877, chi-square test). There was no significant difference between study treatments in the incidence of the secondary efficacy outcome measures. CRC or CRI occurred in 21 (7.1%) subjects in the dalteparin group and eleven (7.6%) in the placebo group.	A total of 1878 AEs were reported in 255 (89.5%) subjects in the dalteparin group, and 887 were reported in 121 (86.4%) subjects in the placebo group. The AE profile was similar in the two treatment groups. Thirty one (10.9%) subjects in the dalteparin group and 18 (12.9%) in the placebo group died. A total of 152 SAEs were reported in 81 (28.4%) subjects in the dalteparin group and 83 in 46 (32.9%) in the placebo. Forty difference subjects in the dalteparin group and 22 (15.7%) in the placebo discontinued because of AEs. Leucopenia and neutropenia occurred more frequently in dalteparin- than in placebo-treated patients (leucopenia: 9.8% vs 5.0%, respectively; neutropenia: 9.8% vs 5.7%, respectively). Dyspnoea was reported more frequently in the dalteparin group: 11.6% subjects vs 3.6% in the placebo group. Epistaxis was reported in 7.0% subjects in the dalteparin group and 4.3% in the placebo.

Outcome measures for Study 98-FRAG-076

The primary efficacy outcome measure was a catheter related complication (CRC) as described in Table 3. The secondary efficacy outcome measures were asymptomatic CRT, catheter-related infection (CRI), clinically relevant non-catheter-related venous or arterial thromboembolic event (TEE). The safety outcome measures were AEs, major haemorrhagic events, minor haemorrhagic events, haematology and coagulation profile. The results of laboratory tests were not recorded unless the results were of grade 3-4 severity and/or supported a study drug-related adverse event.

Statistical analysis for Study 98-FRAG-076

The primary statistical analysis was designed as a test of superiority. Hypothesis tests were performed using the Cochran-Mantel-Haenszel test stratified by catheter insertion site (proximal versus distal to the axilla), and investigational sites. Incidence of the secondary endpoints was compared using the two-sided Fisher's exact test.

The sample size calculation assumed an incidence of CRC in the placebo population of 30%. The treatment groups were in the ratio of two dalteparin subjects for every one placebo subject. A sample size of 290 subjects in the dalteparin group and 145 in the placebo would be required to detect a reduction in risk of 18% in patients treated with dalteparin, with a power of 0.80, and an α of 0.001, using a two-sided hypothesis test. The calculation included

a 15% increase in sample size to account for patients withdrawing early due to events such as chemotherapy toxicity, catheter malfunction, venography refusal, or death.

Results for Study 98-FRAG-076

A total of 439 subjects were randomised to treatment: 294 to dalteparin and 145 to placebo. Fourteen subjects did not receive study treatment. The proportion of subjects discontinuing was similar for the two treatment groups: 94 (33.0%) subjects in the dalteparin group and 46 (32.9%) in the placebo. Of the randomized subjects, 257 (58.5%) were female and 182 (41.5%) were male. Age range was 18 to 90 years. The treatment groups were similar in demographic and coagulation profile.

For the primary efficacy outcome measure, there was a similar incidence of events in both treatment groups: 11 events (3.7%) in the dalteparin group and 5 (3.4%) in the placebo ($p=0.877$, chi-square test) (Table 4). There was no significant difference between study treatments in the incidence of the secondary efficacy outcome measures (Table 5). CRC or CRI occurred in 21 (7.1%) subjects in the dalteparin group and eleven (7.6%) in the placebo group.

Table 4: Frequency of CRC During Study According to the Adjudication Committee's Assessment (ITT Population)

	Dalteparin N=294		Placebo N=145		Total N=439	
	N	%	N	%	N	%
Patients with at least one event	11	3.7	5	3.4	16	3.6
Clinically relevant CRT	10	3.4	5	3.4	15	3.4
CR catheter-related PE	1	0.3	0	0.0	1	0.2
Catheter-related obstruction	0	0.0	0	0.0	0	0.0

Table 5: Frequency of Secondary Endpoints During Study (ITT Population)

	Dalteparin N=294		Placebo N=145		Total N=439	
	N	%	N	%	N	%
Asymptomatic CRT	10	3.4	6	4.1	16	3.6
Catheter-related infection	11	3.7	6	4.1	17	3.9
CR non-catheter-related TEE	3	1.0	1	0.7	4	0.9

TEE: Thromboembolic event

Evaluator's comment

Study 98-FRAG-076 is not supportive of efficacy in this patient group. However, the doses used in the study were less than those used in the Pivotal Study. Hence these findings do not detract from the findings of efficacy in the Pivotal Study.

Safety

Pivotal Study

AEs reported for Study 98-FRAG-069

For **Study 98-FRAG-069** (Table 1), duration of study treatment is summarized in Table 6. A total of 228 subjects were treated with dalteparin, with 110 subjects treated for at least six months. A total of 283 (84.0%) subjects in the dalteparin group and 283 (85.5%) in the OAC

group reported at least one AE. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and ecchymosis occurred more frequently in the dalteparin group (Table 7). The most frequently reported adverse events were nausea (21.4% dalteparin- and 17.5% OAC-treated patients), vomiting (13.6% and 16.0%, respectively), and fatigue (16.0% and 18.7%, respectively). Study drug related AEs were reported in 121 (35.9%) subjects in the dalteparin group and 105 (31.7%) in the OAC group.

Table 6: Duration of Treatment (As-treated Population)

Study Period (months)	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]	

AEs relating to haemorrhage reported for Study 98-FRAG-069

Bleeding events overall were less common in the dalteparin group, 46 (13.6%) subjects compared with 62 (18.5%) subjects in the OAC group. However major bleeding episodes were more common in the dalteparin group and one subject in the dalteparin group died due to a major bleeding episode (Table 8). Two other deaths from bleeding occurred in the dalteparin group: one occurred 20 days after treatment ceased (cerebellar haemorrhage) and the other 81 days (gastrointestinal haemorrhage) after treatment ceased. One subject with colorectal cancer in the OAC group died of bleeding 5 days after treatment discontinuation (melaena). Ten (2.9%) subjects in the dalteparin group and five (1.5%) in the OAC group permanently discontinued treatment due to a major hemorrhagic event. Major bleeding events tended to occur early in treatment. Minor bleeding events were less common in the dalteparin group, 30 (8.9%) subjects compared with 50 (14.9%) in the OAC group. Fifteen (4.4%) subjects in the dalteparin group and seven (2.1%) in the OAC group were reported to have thrombocytopenia related to study medication.

Table 7: Frequency of Treatment-Emergent Adverse Events Reported in $\geq 5\%$ of Patients by System Organ Class and Preferred Term - Any Drug Relationship, 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	%
Blood and Lymphatic System Disorders	Anaemia 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	Oedema 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
	Diarrhoea 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 Administrative 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
Hepatobiliary Disorders	Hypoproteinaemia	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
	GGT increased	53	15.7	23	6.8	39	11.8	17	5.1
	Haemoglobin increased	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
	Hyponatraemia	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
Neoplasms 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
	Dyspnoea 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 and Subcutaneous Tissue Disorders	Ecchymosis	30	8.9	0	0.0	17	5.1	0	0.0

Table 8: Frequency of Adjudicated Major Bleeding Events During Treatment (As-treated Population)

	Dalteparin N=338		OAC N=335	
	N	%	N	%
At least one major bleeding event	19	5.6	12	3.6
Fatal bleeding event	1	0.3	0	0.0
Critical sites	4	1.2	3	0.9
Retroperitoneal	2	0.6	1	0.3
Intracranial	1	0.3	2	0.6
Pericardial	1	0.3	0	0.0
Other	15	4.4	9	2.7

Deaths reported for Study 98-FRAG-069

Death occurred at a similar rate for both treatment groups and was predominantly due to underlying cancer rather than VTE. Death occurred more commonly on treatment for dalteparin, but off treatment for OAC (Table 9). Whilst no explanation for this result is given in the report, it might be due to patients with terminal cancer needing to discontinue an oral treatment, but being able to continue a subcutaneous treatment.

Table 9: 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	0.03	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

Serious Adverse Events (SAEs) and discontinuations due to AEs reported for Study 98-FRAG-069

SAEs were reported in 159 (47.2%) subjects in the dalteparin group and 147 (44.4%) in the OAC group. There were twelve SAEs relating to thrombocytopenia in the dalteparin group and one in the OAC group. Sixty three (18.7%) subjects in the dalteparin group and 62 (18.7%) discontinued because of AEs. Discontinuation because of thrombocytopenia occurred in eight (2.4%) subjects in the dalteparin group and one (0.3%) in the OAC group.

Laboratory safety findings for Study 98-FRAG-069

Other than platelet count, changes in haematological parameters were similar for the two groups. Elevations in activated partial thromboplastin time (aPTT) occurred less frequently in the dalteparin group: 104 (30.8%) subjects compared with 169 (50.4%) in the OAC group. Abnormalities in ALT, AST and gamma-glutamyltransferase (GGT) were more common in the dalteparin group. Sixty (18.3%) subjects in the dalteparin group and 56 (16.7%) in the OAC group had worsening of creatinine.

Evaluator's comments

Major bleeding episodes appear to be more common with dalteparin than with OAC. Overall, major bleeding episodes were more frequently reported and one subject in the

dalteparin group died due to a major bleeding episode. More subjects in the dalteparin group permanently discontinued treatment due to a major hemorrhagic event.

Thrombocytopenia was more common with dalteparin. Fifteen (4.4%) subjects in the dalteparin group and seven (2.1%) in the OAC group were reported to have thrombocytopenia related to study medication. There were twelve SAEs relating to thrombocytopenia in the dalteparin group and one in the OAC group. Discontinuation because of thrombocytopenia occurred in eight (2.4%) subjects in the dalteparin group and one (0.3%) in the OAC group.

Abnormalities in ALT, AST and GGT were more common in the dalteparin group

A total of 228 subjects were treated with dalteparin, with 110 subjects treated for at least six months. Given that the adverse effect profile for dalteparin has been described for the previously registered indications, this is a sufficient number of subjects to demonstrate safety in this subpopulation of patients.

Supportive Study

AEs reported for Study 98-FRAG-076

For *Study 98-FRAG-076* (Table 3), exposure to study medication is summarized in Table 10. A total of 1878 AEs were reported in 255 (89.5%) subjects in the dalteparin group, and 887 were reported in 121 (86.4%) subjects in the placebo group (Table 11). The AE profile was similar in the two treatment groups (Table 12). Leucopenia and neutropenia occurred more frequently in dalteparin- than in placebo-treated patients (leucopenia: 9.8% versus 5.0%, respectively; neutropenia: 9.8% versus 5.7%, respectively). Dyspnoea was reported more frequently in the dalteparin group: 11.6% subjects versus 3.6% in the placebo group. Epistaxis was reported in 7.0% subjects in the dalteparin group and 4.3% in the placebo.

Table 10: Duration of Treatment (As-treated Population)

Duration of Treatment	Dalteparin N=285		Placebo N=140	
	N	%	N	%
<4 weeks	29	10.2	15	10.7
≥4 weeks and <8 weeks	16	5.6	13	9.3
≥8 weeks and <12 weeks	24	8.4	9	6.4
≥12 weeks	215	75.4	102	72.9
Patients completed 16 weeks	191	67.0	94	67.1

Table 11: Frequency of Patients who Complained of at Least One Adverse Event and Number of Adverse Events - Any Relationship or Drug Related (As-treated Population)

	Dalteparin N=265		Placebo N=140	
	N	%	N	%
Patients with at least one AE (any drug relationship)	255	89.5	121	86.4
Number of AEs (any drug relationship)	1878		887	
Average number of AEs per patient with at least one AE (any drug relationship)	7.4		7.3	
Patients with at least one drug-related AE	58	20.4	23	16.4
Number of drug-related AEs	97		34	
Average number of drug-related AEs per patient with at least one drug-related AE	1.7		1.5	

Table 12: Frequency of Treatment-Emergent Adverse Events Reported in $\geq 5\%$ of Patients in at Least One Arm by System Organ Class and Preferred Term - Any Drug Relationship, Worst CTC Grade by Patient (As-treated Population)

System Organ Class	Preferred Term	Dalteparin N=285				Placebo N=140			
		Any grade		Grade 3-4		Any grade		Grade 3-4	
		N	%	N	%	N	%	N	%
Blood and Lymphatic System Disorders	Anaemia NOS	43	15.1	16	5.6	18	12.9	6	4.3
	Febrile neutropenia	13	4.6	9	3.2	8	5.7	8	5.7
	Leucopenia NOS	28	9.8	7	2.5	7	5.0	3	2.1
	Neutropenia	28	9.8	22	7.7	8	5.7	6	4.3
	Thrombocytopenia	17	6.0	11	3.9	9	6.4	5	3.6
Cardiac Disorders	Oedema	20	7.0	2	0.7	8	5.7	0	0.0
Gastrointestinal Disorders	Abdominal pain NOS	19	6.7	3	1.1	13	9.3	5	3.6
	Abdominal pain upper	7	4.9	2	0.7	7	5.0	0	0.0
	Constipation	43	15.1	2	0.7	14	10.0	1	0.7
	Diarrhoea NOS	58	20.4	5	1.8	34	24.3	7	5.0
	Nausea	90	31.6	9	3.2	50	35.7	2	1.4
	Stomatitis	31	10.9	4	1.4	16	11.4	0	0.0
	Vomiting NOS	53	18.6	11	3.9	23	16.4	3	2.1
General Disorders and Administrative Site Conditions	Asthenia	23	8.1	2	0.7	12	8.6	1	0.7
	Fatigue	69	24.2	9	3.2	33	23.6	2	1.4
	Injection site reaction	18	6.3	0	0.0	4	2.9	0	0.0
	Mucosal inflammation NOS	29	10.2	4	1.4	8	5.7	1	0.7
	Pain NOS	16	5.6	3	1.1	4	2.9	1	0.7
	Pyrexia	55	19.3	5	1.8	15	10.7	3	2.1
	Weakness	5	1.8	0	0.0	12	8.6	2	1.4
Infections and	Urinary tract infection NOS	18	6.3	1	0.4	6	4.3	0	0.0

Infestations									
Metabolism and Nutrition Disorders	Anorexia	13	4.6	1	0.4	12	8.6	0	0.0
	Hyponatraemia	12	4.2	1	0.4	8	5.7	0	0.0
Musculoskeletal, Connective Tissue and Bone Disorders	Arthralgia	11	3.9	1	0.4	10	7.1	2	1.4
Neoplasms Benign and Malignant	Carcinoma NOS	14	4.9	8	2.8	8	5.7	5	3.6
Nervous System Disorders	Dizziness	8	2.8	0	0.0	7	5.0	0	0.0
	Headache NOS	17	6.0	1	0.4	6	4.3	1	0.7
	Insomnia NEC	12	4.2	0	0.0	9	6.4	0	0.0
	Paraesthesia NEC	12	4.2	0	0.0	8	5.7	0	0.0
Respiratory, Thoracic and Mediastinal Disorders	Cough	24	8.4	1	0.4	10	7.1	0	0.0
	Dyspnoea NOS	33	11.6	10	3.5	5	3.6	2	1.4
	Epistaxis	20	7.0	0	0.0	6	4.3	0	0.0
Skin and Subcutaneous Tissue Disorders	Alopecia	39	13.7	4	1.4	15	10.7	0	0.0
Vascular Disorders	Hypotension NOS/Hypertension NOS	7	2.5	2	0.7	8	5.7	4	2.9

Deaths, SAEs and discontinuations for Study 98-FRAG-076

Thirty one (10.9%) subjects in the dalteparin group and 18 (12.9%) in the placebo group died. Cause of death was similarly distributed for the two treatment groups (Table 13). A total of 152 SAEs were reported in 81 (28.4%) subjects in the dalteparin group and 83 in 46 (32.9%) in the placebo. Forty (14.0%) subjects in the dalteparin group and 22 (15.7%) in the placebo discontinued because of AEs. There were no results for laboratory tests (haematology, clinical chemistry or coagulation profile) performed during treatment that were included in the study report.

Table 13: Summary of Deaths (As-treated Population)

Primary cause of death	Dalteparin N=285						Placebo N=140					
	On treatment		Off treatment		Total		On treatment		Off treatment		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	5	1.8	26	9.1	31	10.9	3	2.1	15	10.7	18	12.9
Cancer-related	1	0.4	21	7.4	22	7.7	3	2.1	11	7.9	14	10.0
Intercurrent disease	4	1.4	4	1.4	8	2.8	0	0.0	4	2.9	4	2.9
Cardiac disorders	2	0.7	1	0.4	3	1.1	0	0.0	2	1.4	2	1.4
Infections and infestations	1	0.4	2	0.7	3	1.1	0	0.0	0	0.0	0	0.0
Blood and lymphatic system	1	0.4	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0
Respiratory, thoracic and mediastinal disorders	0	0.0	1	0.4	1	0.4	0	0.0	2	1.4	2	1.4

TEE-related	1	0.4	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0
Other	0	0.0	1	0.4	1	0.4	0	0.0	0	0.0	0	0.0

Evaluator's comments

The AE profile for dalteparin was similar to placebo except for a greater incidence of leucopenia and neutropenia. The dose of dalteparin used in **Study 98-FRAG-076** was less than that used in the Pivotal Study and this could explain the lower rates of AEs, particularly the lower rate of thrombocytopenia than that observed in the Pivotal Study.

Post-marketing Experience

Periodic Safety Update Reports 1 December 1999 to 30 November 2004

During this time period there were sales of 268,761,000 standard dosage units of dalteparin. There were 1,857 events reported in 1,211 cases. Sixteen of the reports were from clinical trials and 118 were obtained from literature reports. The most commonly reported events were cerebral haemorrhage, deep vein thrombosis, drug exposure during pregnancy, drug ineffective, gastrointestinal haemorrhage, haematoma, haemorrhage, medication error, pulmonary embolism, thrombocythaemia and thrombocytopenia. AEs that were unexpected included 16 reports of alopecia, five reports of osteoporosis, and five of vasculitis. There were 141 reports of death - including 33 from cerebral haemorrhage, 24 from pulmonary haemorrhage, 14 from haematoma, 13 from haemorrhage, nine from gastrointestinal haemorrhage, eight from thrombocytopenia, eight from drug ineffective, six from retroperitoneal hemorrhage, five from deep vein thrombosis, four from melaena, and four from toxic epidermal necrolysis. Reports of drug interactions involved other drugs affecting blood clotting such as UFH, LMWH, heparinoids, lepirudin, desirudin and/or danaparoid and clopidogrel.

Addendum to the Periodic Safety Update Report 1 December 2004 to 30 June 2007

During this time period there were worldwide sales of 133,883,700 standard dosing units (one syringe, ampoule or vial). There were 1,914 events reported in 1,027 cases (reports) that fulfilled criteria for inclusion. The events included in the report were those spontaneous cases reported by health care professionals and literature non-clinical trial sources, that contain serious adverse events, and non-serious unlisted adverse. In addition, all serious, related cases from Clinical Studies, Post-Authorization Safety Studies (PASS), compassionate/named patient use, and other medically confirmed solicited cases are all included in the report.

There were three reports of osteoporosis or fractures (0.3% of all reports). There were 39 reports of skin adverse effects (erythemas, rashes, eruptions and exanthems; urticarias) representing 3.8% total reports. There were 16 reports of pruritus (1.6% of total reports). There were four cases reporting events of erythema multiforme (2), Stevens-Johnson syndrome (1), or toxic epidermal necrolysis (1). There were 25 reports of vasculitis (2.4% of reports). A fatal outcome was reported in 110 cases (10.7% of total reports). Haemorrhagic events were frequently reported as a cause or contributing factor in these cases.

Summary Bridging Report 1 December 1999 to 31 August 2006

This report used data that were included in the Periodic Safety Update Reports (PSURs). The report covered 1,696 cases between 1 December 1999 and 31 August 2006.

Thrombocytopenia was reported in 178 cases and heparin induced thrombocytopenia was

reported in 35 cases. Gastrointestinal haemorrhage was a common AE: gastrointestinal haemorrhage (36), melaena (25), haematemesis (18), gastric ulcer haemorrhage (9), duodenal ulcer haemorrhage (9), gastric haemorrhage (2). There were 59 reports of cerebral haemorrhage. There were no additional previously unrecognised AEs attributable to dalteparin.

Evaluator's comments

The PSURs confirm the known adverse effect profile of dalteparin. The most important AEs involved bleeding and/or thrombocytopenia.

Clinical Summary and Conclusions

Conclusions

Dalteparin was demonstrated to reduce the recurrence of VTE over a period of 6 months in patients with cancer and with symptomatic VTE (proximal venous thrombosis and/or pulmonary embolism). Dalteparin was clearly superior to OAC for the primary efficacy outcome measure used in the Pivotal Study (*Study 98-FRAG-069*). However, the primary efficacy outcome measure might not be the most appropriate efficacy outcome measure. Although dalteparin decreased the risk of DVT or PE it did not alter the risk of death. It is not clear from the study whether the disease burden for the subjects or health resource utilisation were altered by the treatment. The results of the quality of life measure did not help resolve this issue.

With the exceptions of the primary efficacy outcome measure (which did not include death in the outcome measure) and the open study design the Pivotal Study appears to have been conducted according to CPMP guidance.^{1,2} There are provisions in the guidance for conducting open trials where blinding is impractical. This is the case when OAC is used as the comparator because the need for monitoring INR would lead to unblinding.

However, because death was not included in the primary efficacy outcome measure the results of the study are still open to interpretation with regard to the benefit to patients. Dalteparin may decrease the risk of VTE, but there is no clear improvement in quality of life (reflecting overall morbidity) or in mortality. There is also the increased risk of haemorrhage with dalteparin. Hence the risk benefit profile is also open to interpretation.

Although the treatment effect was primarily for DVT rather than PE, both were included in the composite primary efficacy outcome measure, for which the study was powered. PE was a less common outcome in the study population and to have demonstrated a difference between the treatments, independently for the outcome of PE, would have required a much larger sample size. Hence it is reasonable to include both conditions in the indications.

Study 98-FRAG-076 was not supportive of efficacy in this patient group. However, this might be explained by the doses used in the study being less than those used in the Pivotal Study. Hence these findings do not detract from the findings of efficacy in the Pivotal Study.

With regard to safety, major bleeding episodes appear to be more common with dalteparin than with OAC. Overall, major bleeding episodes were more frequently reported and one subject in the dalteparin group died due to a major bleeding episode. More subjects in the dalteparin group permanently discontinued treatment due to a major hemorrhagic event.

Thrombocytopenia was more common with dalteparin. Fifteen (4.4%) subjects in the dalteparin group and seven (2.1%) in the OAC group were reported to have thrombocytopenia related to study medication. There were twelve SAEs relating to thrombocytopenia in the dalteparin group and one in the OAC group. Discontinuation because of thrombocytopenia occurred in eight (2.4%) subjects in the dalteparin group and one (0.3%) in the OAC group.

Abnormalities in ALT, AST and GGT were more common in the dalteparin group

In the supportive study (*Study 98-FRAG-076*) the AE profile for dalteparin was similar to placebo except for a greater incidence of leucopenia and neutropenia. However, the dose of

dalteparin was less than that used in the Pivotal Study and this could explain the lower rates of AEs, particularly the lower rate of thrombocytopenia.

The post-marketing data do not identify any treatment related AEs that were not currently mentioned in the Product Information document. The PSUR confirmed the known adverse effect profile of dalteparin. The most important AEs involved bleeding and/or thrombocytopenia.

With regard to the risk benefit assessment for dalteparin for the indication of:

Extended treatment of symptomatic venous thromboembolism [VTE] (proximal venous thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with cancer;

on balance, the benefit of reduced risk of VTE would appear to outweigh the increased risk of haemorrhage.

Deficiencies in the Submission

The Pivotal Study was an open design. The study could have been conducted using a double dummy design, but the monitoring of INR would have made maintenance of blinding extremely difficult. Hence the use of OAC as the comparator group made maintenance of blinding unlikely. OAC would be the usual treatment for this patient group and is therefore the most appropriate comparator treatment. The use of strict criteria in defining the outcome measure, and the use of blinded assessment of outcome, compensate to some degree for the open study design.

Mortality was not included as an endpoint in the primary efficacy outcome measure. The sponsor argued that mortality in this patient group is high due to cancer mortality. This was in fact the case in the Pivotal Study. However, the sponsor could have performed a secondary analysis that included mortality in a composite outcome measure.

The conduct of the quality of life measure in the Pivotal Study was suboptimal. There was a high rate of missed assessments. The measure was administered on a subgroup of the study population, rather than the entire study population, and might not have had sufficient power to detect a difference between treatments. The provision of more complete data might have helped in the risk benefit assessment.

Laboratory tests were not reported in the supportive study. Only results that were of grade 3-4 severity and/or supported a study drug-related adverse event were to have been recorded. However, this precludes the analysis of mean changes in laboratory parameters, or results of lesser significance.

Recommendations

The application should be approved and the Indications for dalteparin should be extended to include:

Extended treatment of symptomatic venous thromboembolism [VTE] (proximal venous thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with cancer.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in an application of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in an application of this type.

Clinical

Clinical Evaluation

The clinical data relies on the pivotal study called CLOT (Comparison of Low molecular weight heparin (dalteparin) versus Oral anticoagulant Therapy for long term anticoagulation in cancer patients with venous thromboembolism) to support the new indication in 676 patients for 6 months. A supportive study was also submitted in cancer patients with central venous catheters to prevent catheter related complications, along with 4 post-marketing reports. The clinical evaluator recommended approval.

The issues noted by the evaluator included:

- Mortality was not included in the primary endpoint and the data did not demonstrate a reduction in the risk of death, even though a reduction in VTE was seen.
- The data do not demonstrate a reduction in the disease burden or health resource utilisation and the quality of life measure did not assess these issues.
- The CLOT study followed EU guidelines however it did not include death as an assessment and was of open label design, although the latter is acceptable given INR monitoring would make oral anticoagulant blinding impractical.
- The primary composite endpoint was primarily driven by DVT rather than PE, but it would be appropriate to include both in the indication since it was a pre-defined component of the endpoint and would require a much larger sample size to show independent benefit for PE alone.
- Increased risk of major bleeding with dalteparin, including discontinuation due to major bleeding.
- Thrombocytopenia and abnormalities in liver function were more common on dalteparin than oral anticoagulants.

Efficacy

98-FRAG-069 (CLOT): This was a multicentre, multinational, phase 3, randomised, open label, active controlled parallel group superiority trial of dalteparin (dose as per PI) versus coumarin (INR of 2-3 with dalteparin cover for at least 5 days until stable INR) for 6 months in 676 cancer patients ≥ 16 years of age with acute symptomatic proximal limb DVT and/or PE. Patients were either hospitalised or outpatients with active malignancy (excluding skin cancer) defined as a diagnosis of cancer or treatment for it in the last 6 months, current treatment for cancer at randomisation or documentation of recurrent or metastatic disease. Proximal limb DVT was defined using venography or ultrasonography and PE by angiogram, V/Q scan or spiral CT scan. Baseline characteristics were similar in both groups, including tumour type, status and treatment, VTE characteristics (69% DVT only, 19% PE only and 12% both), VTE risk factors and co-medications. The dose of dalteparin was reduced in

thrombocytopenia and renal impairment. Study completion was 53% on dalteparin versus 49% on coumarin with the main reasons for discontinuing being death due to cancer (15.4 versus 5.1%) and confirmed VTE (6.2 versus 14%). The primary efficacy endpoint, a composite of symptomatic recurrent lower limb DVT or PE or both during the 6 months following occurred in 8% (27 patients) on dalteparin versus 15.7% (53 patients) on coumarin. A significant 52% risk reduction in VTE recurrence at 6 months was seen with dalteparin compared to coumarin (RR= 0.48, 95% CI 0.30-0.77, p=0.0016). The benefit was derived in the first month and maintained thereafter and was predominantly in patients with solid tumours that were metastatic. An analysis by prognostic factors showed benefit for dalteparin over coumarin was numerically higher in most groups except notably those with haematological malignancies (4 versus 0 patients with VTE) and non-metastatic malignancies (7 versus 5 patients with VTE) where the frequency of first recurrent VTE was higher on dalteparin. Secondary efficacy measures showed no difference in time to death or risk of death at 6 or 12 months (although slightly less on dalteparin). Quality of life assessment in a subgroup with only 40% completion of assessment showed no difference between groups except for benefit for dalteparin in social functioning but more nausea, vomiting and diarrhoea than coumarin.

98-FRAG-076: This was a 16 week, multinational, multicentre, phase 3, randomised, double blind, placebo controlled study in 439 cancer patients who required a central venous catheter for chemotherapy to assess catheter related thromboses, catheter related PE or catheter related obstruction. The study used a standard dose of dalteparin of 5000 IU injection versus normal saline and did not show a difference in the primary outcome (3.7 versus 3.4%).

Safety

Total exposure to dalteparin in the pivotal study was 338 patients with 110 for at least 6 months. Adverse events most common were nausea, vomiting and fatigue with ALT elevations (11.9 versus 6.6%), AST elevations (8.9 versus 5.4%), injection site reactions (11.6 versus 3%), thrombocytopenia (11 versus 8.2%) and ecchymoses (8.9 versus 5.1%) higher on dalteparin. Bleeding overall was less on dalteparin (13.6 versus 18.5%) but major bleeding was higher (5.6 versus 3.6%) including one death on dalteparin due to major bleeding. Two other deaths from major bleeding occurred on dalteparin post treatment cessation and one on coumarin. Discontinuation due to major bleeding was also higher on dalteparin (2.9 versus 1.5%). Deaths during the 6 months were similar overall (56.2 versus 57.9%) but higher on-treatment for dalteparin and higher off-treatment for coumarin. Serious adverse events were slightly higher on dalteparin and included thrombocytopenia (12 versus 1 event). Laboratory changes showed thrombocytopenia, elevations in liver enzymes and worsening of creatinine more commonly on dalteparin. The supportive study showed higher leucopenia, neutropenia, dyspnoea and epistaxis on dalteparin. The post-marketing data were supportive of the current safety profile of dalteparin.

Risk-Benefit Analysis

Efficacy

The data demonstrated a significant superiority for dalteparin over coumarins in reducing the recurrence of symptomatic VTE in cancer patients over the 6 month period. This mainly occurred during the first month of treatment and was maintained thereafter. However this benefit was only seen in patients with solid tumours and not those of haematological origin and was only seen in patients with metastatic disease and not those with non-metastatic tumours, although the number of VTE events was low in these subgroups. The benefit was also mainly in DVT recurrence rather than PE and no benefit in terms of mortality reduction was seen. Efficacy has not been evaluated beyond 6 months, therefore it is unclear if benefit

is maintained beyond this period, especially during cancer progression. The supportive study did not demonstrate efficacy for dalteparin over placebo, but had a different indication and used a lower dose.

Safety

The pivotal trial noted higher major bleeding (including one death on dalteparin), liver enzyme elevations, thrombocytopenia, ecchymoses and worsening creatinine on dalteparin compared with coumarin, however bleeding overall was less on dalteparin. The safety data are essentially limited to 6 months duration and therefore it is unclear if safety remains acceptable beyond this period or if the coagulation profile and bleeding risk could change with metastases, for example hepatic.

Data deficiencies

The primary endpoint should have included mortality, as is usual in studies in VTE and as per the EU guidelines. The sponsor has indicated that assessing mortality would have been difficult given the higher mortality in cancer patients. Whilst this may be true depending on the selection of patients and was true in the CLOT study where mortality was high, the sponsor could have assessed all deaths for those that may be related to VTE as a secondary composite endpoint. The open label design is not ideal but INR monitoring would have made blinding unlikely. The use of strict criteria to define outcome measures and blinded assessment helps to partially mitigate this concern. The quality of life assessment was sub-optimal and further effort should have been made to assess patients given the high rate of missed assessments and use of only a subset of the population for assessment. There was no dose response study to determine the optimal dose for this group and the duration of data are limited to 6 months which makes it unclear for clinicians on whether benefit is maintained beyond this period on or off treatment. The EU guideline refers to studies being of 6-12 months duration and the sponsor has addressed this through a statement in the PI that safety and efficacy beyond 6 months has not been evaluated. There is a lack of data in children and insufficient data by different malignancy categories (that is, metastatic versus non-metastatic, solid tumours versus haematological). No new drug interaction studies were presented with medications to treat cancer.

Post-registration commitments

The sponsor has committed to providing the FDA with post-market study commitments that include a study in paediatric cancer patients that covers all age ranges and a study in cancer patients (both metastatic and non-metastatic) receiving extended treatment for more than 6 months that includes patients with renal impairment (including severe renal impairment). It was requested that the sponsor provide these to the TGA when complete for evaluation.

Validity of the comparator

Although warfarin is not specially registered in Australia for use in cancer patients, it does have a general indication of prophylaxis and treatment of venous thrombosis and its extension, and pulmonary embolism.

Summary

The data have demonstrated that dalteparin is superior to coumarin in reducing the recurrence of VTE (primarily DVT) in cancer patients (especially solid tumours and metastatic disease) with VTE, however there is no benefit in terms of mortality reduction and a higher risk of major bleeding along with other safety findings such as thrombocytopenia. The data are also not clearly supportive of treatment in patients with haematological cancers or non-metastatic disease and are limited to 6 months duration. The lack of clear benefit in haematological

cancers along with the subsequent increased risk of bleeding compared to coumarin suggests the indication should be restricted to solid tumours only. Although a clear benefit was also not seen in non-metastatic tumours, the efficacy was similar to coumarin. Both of these subgroups have small numbers of patients, therefore the evidence for benefit and risk is less clear. The risk benefit profile beyond 6 months is also unknown. Although no clear benefit has been seen in PE reduction, given it is a component of VTE and unlikely to have sufficient power to demonstrate a benefit by itself, then it would be appropriate to include it in the indication. The lack of inclusion of mortality in the primary endpoint is a deficiency even though assessment might have been hampered by the high mortality seen in the study.

The Delegate proposed to approve the submission to extend the indications for dalteparin for the treatment of patients with cancer to reduce the recurrence of VTE in patients with symptomatic VTE, based on the safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk/Benefit discussion:

Extended treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence of VTE in patients with solid cancer tumours

The sponsor should address the following issues in their Pre-ADEC response:

- Confirmation of a post-market commitment to submit the results of two studies in paediatric cancer patients and long term safety and efficacy in cancer patients, including renal impairment, upon completion for evaluation by the TGA. This commitment will form a condition of registration.
- Provide a justification for use in patients with non-metastatic disease and haematological malignancies, given the higher rate of VTE and adverse effects compared to coumarin, and identify if any further trials are being conducted in this setting.
- Are there any further data to support the safety and efficacy of dalteparin in this setting for treatment beyond 6 months?

The Delegate also addressed the following questions to the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC):

- Should Fragmin be approved in the subgroup of patients with haematological cancers, given the higher rate of VTE recurrence compared to coumarin? Are patients with haematological malignancies at higher risk of bleeding than patients with solid tumours?
- Should Fragmin be approved in the subgroup of patients with non-metastatic tumours, given the slightly higher rate of VTE recurrence compared to coumarin?
- Should use be restricted to adults only, given study participants were 22-89 years?
- Should there be a limitation on the treatment duration given the data from the C LOT study is only up to 6 months? The PI advises that safety and efficacy data have not been evaluated beyond 6 months.

Having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, the ACPM agreed with the Delegate's proposal and recommended the following indication:

Extended treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence of VTE in patients with solid tumour cancers

In making this recommendation, the Committee noted that there are few patients in the pivotal study with haematological cancers and they were lymphoma and myeloma patients

rather than leukaemia patients. However, there was a higher rate of VTE recurrence compared to coumarin, and therefore recommended that the indication be limited to patients with solid tumour cancers.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Fragmin injection syringes containing dalteparin sodium 2500 Anti-Xa IU/0.2 mL, 5000 Anti-Xa IU/0.2 mL, 7500 Anti-Xa IU/0.75 mL, 10000 Anti-Xa IU/1 mL, 12500 Anti-Xa IU/0.5 mL, 15000 Anti-Xa IU/0.6 mL and 18000 Anti-Xa IU/0.72 mL for the new indication:

Extended treatment of symptomatic venous thromboembolism (VTE) (proximal deep vein thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with solid tumour cancers.

Attachment 1. Product Information

PRODUCT INFORMATION

FRAGMIN[®] Injection

Dalteparin sodium

NAME OF THE MEDICINE

Active ingredient: Dalteparin sodium

CAS number: 9041-08-1

DESCRIPTION

Dalteparin sodium (low molecular weight heparin), sodium chloride q.s. (in the 2 500 IU/0.2 mL, 7 500 IU/0.75 mL and 10 000 IU/1 mL syringe presentations only), water for injections.

The active substance of FRAGMIN is the sodium salt of low molecular weight heparin extracted from the intestinal mucosa of pig and is manufactured by controlled depolymerisation of heparin to produce sulphated polysaccharide chains having an average molecular weight of 5000 Da with 90% between 2000 - 9000 Da.

One unit anti-Xa of FRAGMIN is equivalent in effect to the activity of one unit of the 1st international standard for Low Molecular Weight Heparin with regard to inhibition of coagulation factor Xa in plasma.

The 10 000 IU (anti-Xa)/1 mL syringe, 7 500 IU (anti-Xa)/0.75 mL syringe, 5 000 IU (anti-Xa)/0.2 mL syringe and 2 500 IU (anti-Xa)/0.2 mL syringe have the following anti-IIa factor potencies 3900, 2940, 1960 and 980 respectively.

The 0.5, 0.6 and 0.72 mL single dose syringe presentations have the same anti-IIa factor potency per mL as the 5 000 IU (anti-Xa)/0.2 mL single dose syringe, corresponding to 4900, 5880 and 7060 IU anti-IIa respectively per syringe.

PHARMACOLOGY

FRAGMIN is composed of molecules with and without the specially characterised pentasaccharide (the antithrombin binding site). FRAGMIN therefore acts antithrombotically by accelerating the rate of the neutralisation of certain activated coagulation factors largely Factor Xa, but also Factor XIIa and Kallikrein by antithrombin. Other mechanisms may also be involved. Coagulation time, e.g. Activated Partial Thromboplastin Time (APTT), and inhibition of thrombin are influenced to only a small degree. Compared with heparin, FRAGMIN has relatively little effect on platelet function and adhesion and thus has little effect on primary haemostasis. In addition, some of the antithrombotic properties of FRAGMIN are thought to be mediated through the effect on the vessel wall or the fibrinolytic system.

Half-life after intravenous injection is two hours and after subcutaneous injection is 3 - 4 hours. Bioavailability is approx 90% after subcutaneous injection. Pharmacokinetic activity is not dose dependent with regard to anti-Xa half-life within the therapeutic interval.

CLINICAL TRIALS

Unstable Coronary Artery Disease (Unstable Angina and Non-ST-Elevation Myocardial Infarction)

In a double-blind, randomised, placebo-controlled clinical trial, patients who recently experienced unstable angina with ECG changes or non-ST-elevation myocardial infarction were randomised 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 ECG 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-randomised and all-treated patients. The combined incidence of death, myocardial infarction (MI), need for intravenous (i.v.) heparin or i.v. glyceryl trinitrate, and revascularisation was also lower for FRAGMIN than for placebo (see table below).

Efficacy of FRAGMIN in the Prophylaxis of Ischaemic Complications in Unstable Angina and Non-ST-Elevation 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-ST-Elevation 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. glyceryl trinitrate, Revascularisation	59/739 (8.0) ¹	106/756 (14.0)

¹ p-value = 0.001

In a second randomised, 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).

There are insufficient data regarding the benefits from treatment beyond 6 days.

Prolonged Thromboprophylaxis in Orthopaedic Surgery

Two placebo-controlled studies conducted in Denmark and Norway with a total of 496 patients have been performed to study the effect and safety of extended thromboprophylaxis after hip replacement surgery. FRAGMIN 5 000 IU was given subcutaneously once daily up to 35 days postoperatively and was compared with placebo. In both studies FRAGMIN achieved a significant reduction of the frequency of phlebographically detected venous thrombosis. None of the patients receiving FRAGMIN developed pulmonary embolism (PE) in either of the studies, while two cases of PE were reported in the placebo group of the Norwegian study. The difference in the incidence of PE between the FRAGMIN and placebo groups was not significant. There were no serious haemorrhagic complications.

Patients with Cancer and Acute Symptomatic Venous Thromboembolism

In a prospective, multicentre, open-label, clinical trial (CLOT* study), 676 patients with cancer and newly diagnosed, objectively confirmed acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were studied. Patients were randomised to either FRAGMIN 200 IU/kg (max 18 000 IU subcutaneously (s.c.) daily for one month) then 150 IU/kg (maximum 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 (OAC) for six months. In the OAC arm, oral anticoagulation was adjusted to maintain an International Normalised Ratio (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 tumours were: gastrointestinal tract (23.7%), genitourinary (21.5%), breast (16%), lung (13.3%), haematological tumours (10.4%) and other tumours (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 below). The benefit was maintained over the 6-month study period.

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

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) sc 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 5-7 days and OAC for 6 months (target INR 2-3)		
	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
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 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 randomised 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 favour of the FRAGMIN arm, with most of the treatment difference evident in the first month.

There was no significant difference in mortality between the two groups in deaths at 6 and 12 months (131 vs. 137 and 190 vs. 194 in the dalteparin and OAC arms, respectively).

INDICATIONS

Prophylaxis against thrombotic complications during haemodialysis and treatment of acute deep vein thrombosis (DVT).

Extended treatment of symptomatic venous thromboembolism (VTE) (proximal deep vein thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with solid tumour cancers.

Treatment of unstable coronary artery disease, i.e. unstable angina and non-ST-elevation myocardial infarction (also known as non-Q-wave myocardial infarction).

Prophylaxis against thromboembolic complications in the peri- or postoperative period of surgery.

CONTRAINDICATIONS

Hypersensitivity to FRAGMIN or other low molecular weight heparins and/or heparins, or pork products, e.g. history of confirmed or suspected immunologically mediated heparin-induced thrombocytopenia.

Ulcerative conditions showing a tendency to haemorrhage (e.g. gastrointestinal ulcer, ulcerative colitis). Cerebral haemorrhage. Severe coagulation disorder.

Septic endocarditis.

Sympathetic block. Spinal and epidural puncture (FRAGMIN in the dosage of 2 500 – 5 000 IU can however be used as a thromboprophylactic; see **PRECAUTIONS**).

FRAGMIN should not be used following injuries to or surgery involving brain, spinal cord, eye or ears.

In patients being treated for venous thromboembolism (VTE) or unstable coronary artery disease where the patients receive high doses of FRAGMIN, regional anaesthesia is contraindicated due to an increased risk of bleeding.

Since it is derived from heparin, it cannot be excluded that the same contraindications are valid also for FRAGMIN, viz: haemorrhagic diathesis, haemorrhagic stroke, severe hypertension, endocarditis lenta.

It is not known whether FRAGMIN passes the placental barrier.

PRECAUTIONS

When neuraxial anaesthesia (epidural/spinal anaesthesia) 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 haematoma 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 haemostasis 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 monitored frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment (decompression) is necessary. The physician should consider the potential benefit versus the risk before neuraxial intervention in patients anticoagulated for thromboprophylaxis.

As low molecular weight heparins are unique and separate entities with regard to potency, kinetics and possibly modes of action, these products are not interchangeable clinically.

Dalteparin cannot be used interchangeably (unit for unit) with unfractionated heparin, other low molecular weight heparins, or synthetic polysaccharides. Each of these medicines differ in their starting raw materials, manufacturing process, physico-chemical, biological, and clinical properties, leading to differences in biochemical identity, dosing, and possibly clinical efficacy and safety. Each of these medicines is unique and has its own instructions for use.

Limited data are available regarding the safety and efficacy of antithrombotic therapy in patients with primary or metastatic tumours of the brain who develop concurrent thromboembolic events. There is a risk of fatal intracranial bleeding with use of

anticoagulation in this category of patients. Therefore, if the treatment with FRAGMIN was considered, it should be monitored closely with regular re-assessment of the status of tumour involvement of the brain and other individual risks.

Prosthetic Heart Valves

Cases of prosthetic valve thrombosis have been reported in patients who have received low molecular weight heparins for thromboprophylaxis. Some of these patients were pregnant women in whom thrombosis led to maternal and/or foetal deaths. Pregnant women are at higher risk of thromboembolism (see **Use in Pregnancy**). FRAGMIN is not approved for use in prosthetic heart valve thromboprophylaxis.

Thrombocytopenia

Thrombocytopenia of any degree should be monitored closely. Special precautions should be taken with FRAGMIN use in conjunction with thrombocytopenia or disorders of platelet function. It is recommended that platelets be counted before starting treatment with FRAGMIN and monitored regularly. Special caution is necessary in rapidly developing thrombocytopenia and severe thrombocytopenia ($<100,000/\mu\text{L}$) during administration of FRAGMIN. In these patients a positive or unknown result with *in vitro* tests for antiplatelet antibody in the presence of FRAGMIN or other low molecular weight heparins and/or heparins contraindicates FRAGMIN (see **CONTRAINDICATIONS**).

In FRAGMIN clinical trials supporting non-cancer indications, platelet counts of $<100,000/\mu\text{L}$ and $<50,000/\mu\text{L}$ 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 $<100,000/\mu\text{L}$ occurred in 13.6% of patients, including 6.5% who also had platelet counts less than $50,000/\mu\text{L}$. 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 oral anticoagulant (OAC) arm. FRAGMIN dose was decreased or interrupted in patients whose platelet counts fell below $100,000/\mu\text{L}$.

Haemorrhage

FRAGMIN should be used with caution in patients who have a potentially higher risk of haemorrhage, such as patients with cancer, thrombocytopenia, platelet disorders, severe liver or kidney insufficiency, and in the thromboprophylaxis and treatment of patients with uncontrolled hypertension or hypertensive or diabetic retinopathy, and in patients receiving concurrent anticoagulant/antiplatelet agents. High doses of dalteparin, such as those needed to treat deep vein thrombosis, pulmonary embolism or unstable coronary artery disease should be used with caution in patients who had a recent surgical procedure.

Higher doses probably carry an increased risk of postoperative bleeding (about two-fold compared with standard heparin), so that the prescribing clinician will need to balance the opposing probabilities of enhanced efficacy versus increased bleeding in forming a judgement about the appropriate dose in an individual patient. The anticoagulant effect of FRAGMIN is enhanced by concurrent treatment with antithrombin III and fresh frozen plasma in patients

with hereditary antithrombin III deficiency, thus in order to avoid bleeding, reduced dosage of FRAGMIN is recommended.

If a transmural myocardial infarction occurs in patients with unstable coronary artery disease, i.e. unstable angina and non-ST-elevation myocardial infarction, thrombolytic treatment might be appropriate. However, since combined FRAGMIN and thrombolytic therapy confers a high risk of major bleeding events, patients who develop ST-elevation myocardial infarction should cease FRAGMIN therapy and commence thrombolytic therapy in combination with aspirin.

Hyperkalaemia

Heparin and low molecular weight heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium or taking potassium sparing drugs. Plasma potassium should be measured in patients at risk.

Osteoporosis

Long term treatment with heparin has been associated with a risk of osteoporosis. The risk of osteoporosis with dalteparin cannot be excluded. Caution should be observed in patients with known osteoporosis and spontaneous fractures.

Monitoring Anti-Xa Levels

Monitoring of the anticoagulant effect of dalteparin is generally not necessary but should be considered for specific patient populations such as those with cancer, renal failure, those who are very thin or morbidly obese, pregnant or those at increased risk of bleeding or rethrombosis.

Patients with severely disturbed hepatic function, significant renal failure or chemotherapy induced thrombocytopenia may need a reduction in dosage and should be monitored accordingly.

Do not administer by the intramuscular route.

Carcinogenicity

No carcinogenicity tests have been performed with this agent.

Use in Pregnancy - Category C (same as standard heparin)

The use of heparin in pregnancy has the usual risks for the mother, in particular osteoporosis and thrombocytopenia. Although heparin does not cause malformations, an increased incidence of human foetal loss and prematurity associated with haemorrhage has been reported.

There are also post-marketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving low molecular weight heparins for thromboprophylaxis. These events led to maternal death or surgical interventions.

Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of low molecular weight heparins or unfractionated heparin.

FRAGMIN is not approved for use in prosthetic heart valve thromboprophylaxis.

Use in Lactation

Not recommended for lactating women as there is limited data available as to whether FRAGMIN passes into breast 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 low molecular weight heparin is extremely low the clinical implications, if any, of this small amount of anticoagulant activity on the breastfeeding infant are unknown.

Use in the Elderly

FRAGMIN should be used with caution in the elderly. Elderly patients (especially patients aged eighty years and above) may be at an increased risk for bleeding complications within the therapeutic dosage ranges. Careful clinical monitoring is advised.

Paediatric use

FRAGMIN should not be used in children. There is limited safety and efficacy information on the use of dalteparin in paediatric patients.

Carcinogenicity

No carcinogenicity tests have been performed with this agent.

Interactions with Other Medicines

As with heparin therapy, the following interactions with other drugs may occur:

1. Enhancement of anticoagulant effect by thrombolytic agents, aspirin and other NSAIDs with effects on platelets, vitamin K antagonists, dipyridamole, Dextran, sulphinpyrazone, probenecid, ethacrynic acid and cytostatics. However, unless specifically contraindicated, patients with unstable coronary artery disease (unstable angina and non-ST-elevation myocardial infarction), should also receive oral low dose aspirin.
2. Reduction of anticoagulant effect by antihistamines, digitalis glycosides, tetracycline and ascorbic acid.

Because NSAIDs and aspirin analgesic/anti-inflammatory doses reduce production of vasodilatory prostaglandins, and thereby renal blood flow and the renal excretion, particular

care should be taken when administering dalteparin concomitantly with NSAIDs or high dose aspirin in patients with renal failure.

Effects on Laboratory Tests

A non-specific increase of hepatic enzymes (AST/SGOT, ALT/SGPT, GGT) has been reported. It is of the same magnitude as occurs with standard heparin and is reversible.

In FRAGMIN clinical trials supporting non-cancer indications where hepatic transaminases were measured, asymptomatic increases in transaminase levels (AST/SGOT and ALT/SGPT) 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 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.

Effects on ability to Drive and Use Machines

Fragmin does not affect the ability to drive or operate machinery.

ADVERSE EFFECTS

In the table below, the adverse reactions are listed by system organ class and frequency:

- very common ($\geq 1/10$)
- common ($\geq 1/100$ to $< 1/10$)
- uncommon ($\geq 1/1,000$ to $< 1/100$)
- rare ($\geq 1/10,000$ to $< 1/1,000$)
- very rare ($< 1/10,000$)
- not known (cannot be estimated from the available data).

Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

Adverse events associated with dalteparin therapy in patients participating in controlled clinical studies are listed in the table below.

MedDRA System Organ Class	Frequency	Adverse event
Blood and lymphatic system disorders	Common	Reversible non-immunologically-mediated thrombocytopenia (type I)
	Rare	Immunologically-mediated heparin-induced thrombocytopenia (type II, with or without associated thrombotic complications – arterial and/or thrombosis or thromboembolism)
Immune system disorders	Uncommon	Allergic reactions
	Rare	Fever
Endocrine disorders	Uncommon	Hyperkalaemia
Vascular disorders	Common	Haemorrhage (bleeding at any site) especially at high doses
Hepatobiliary disorders	Common	Transient slight to moderate elevation of liver transaminases (AST/SGOT, ALT/SGPT, GGT)
Renal and Urinary Disorders	Unknown	Increased serum creatinine
Skin and subcutaneous tissue disorders	Uncommon	Rash , urticaria, pruritus
	Rare	Bullous eruptions, skin necrosis, alopecia
Musculoskeletal and connective tissue disorders	Uncommon	Osteoporosis
General disorders and administration site conditions	Uncommon	Pain at injection site
	Common	Haematoma at injection site

Unstable Angina and Non-ST-Elevation Myocardial Infarction

The table below summarises the major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-ST-elevation myocardial infarction.

Major Bleeding Events in Unstable Angina and Non-ST-Elevation Myocardial Infarction

Indication	Dosing Regimen		
	<u>FRAGMIN</u>	<u>Heparin</u>	<u>Placebo</u>
Unstable Angina and Non-ST-Elevation MI	120 IU/kg/12 hr s.c. ¹	i.v. and s.c. ²	every 12 hr s.c.
	n (%)	n (%)	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 haemoglobin of ≥ 20 g/L 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

The table below summarises:

- all major bleeding events
- 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.

Bleeding Events Following Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	<u>FRAGMIN</u> ²	<u>Warfarin Sodium</u> ¹ oral	<u>FRAGMIN</u> ⁴	<u>Heparin</u>
	5000 IU once daily s.c.		5000 IU once daily s.c.	5000 IU three times a day s.c.
	n (%)	n (%)	n (%)	n (%)
Major Bleeding Events ³	7/274 (2.6)	1/279 (0.4)	0	3/69 (4.3)

Other Bleeding Events ⁵				
Haematuria	8/274 (2.9)	5/279 (1.8)	0	0
Wound Haematoma	6/274 (2.2)	0	0	0
Injection Site Haematoma	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 Normalised 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) haemorrhage caused a significant clinical event, 2) it was associated with a haemoglobin decrease of ≥ 20 g/L 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 haemorrhage.

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 haematoma (one requiring reoperation), three were bleeding from the operative site, one was intra-operative bleeding due to vessel damage, and one was gastrointestinal bleeding. None of the patients experienced retroperitoneal or intracranial haemorrhage 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.

Patients with Cancer and Acute Symptomatic Venous Thromboembolism

The table below summarises 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 met one the following criteria:

1. accompanied by a decrease in haemoglobin of ≥ 20 g/L 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
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 oral anticoagulant (OAC) arm experienced any bleeding event. One bleeding event (haemoptysis in a patient in the FRAGMIN arm at Day 71) was fatal.

Bleeding Events (major and any) (As Treated Population¹)

Study period	<u>FRAGMIN</u>			<u>OAC</u>		
	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 5-7 days and OAC for 6 months (target INR 2-3)		
	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.

Post-Marketing Experience

Blood and Lymphatic System Disorders: A small number of immunologically-mediated heparin-induced thrombocytopenia (type II) with or without associated thrombotic complications (arterial and/or venous thrombosis or thromboembolism) have been reported.

Immune System Disorders: anaphylactic reactions.

Endocrine Disorders: hypoaldosterism.

Cardiac Disorders: prosthetic cardiac valve thrombosis.

Nervous System Disorders: intracranial bleeds have been reported and some have been fatal.

Gastrointestinal Disorders: retroperitoneal bleeds have been reported and some have been fatal.

Skin and Subcutaneous Tissue Disorders: skin necrosis, alopecia, rash

Vascular Disorders: haemorrhage (bleeding at any site), some cases reported have been fatal.

Injury, poisoning and procedural complications: Spinal or epidural haematoma.

DOSAGE AND ADMINISTRATION

Thromboprophylaxis in conjunction with surgery

2 500 IU administered subcutaneously 1–2 hours before the operation and thereafter 2 500 IU subcutaneously each morning until the patient is mobilised, in general 5–7 days.

Thromboprophylaxis in conjunction with general surgery associated with high risk of thrombosis (e.g. malignancy)

5 000 IU is given subcutaneously the evening before the operation and 5 000 IU subcutaneously the following evenings. As an alternative 2 500 IU subcutaneously 1–2 hours before operation and 2 500 IU subcutaneously twelve hours later. On the following days 5 000 IU subcutaneously each morning. Treatment is continued until the patient is mobilised, in general 5–7 days.

Prolonged thromboprophylaxis in orthopaedic surgery (e.g. hip replacement surgery)

Additional risk factors for developing venous thromboembolism, such as previous DVT or PE, malignancy, advanced age, family history, obesity and immobilisation should be considered.

5 000 IU is given subcutaneously the evening before the operation and 5 000 IU subcutaneously the following evenings. Treatment is continued for five postoperative weeks.

As an alternative 2 500 IU is given subcutaneously 1–2 hours before the operation and 2 500 IU subcutaneously 8–12 hours later. On the following days, 5 000 IU s.c. each morning for five postoperative weeks.

Treatment of acute deep vein thrombosis

For patients with acute deep vein thrombosis FRAGMIN can be given either as a continuous i.v. infusion or as twice daily s.c. injections.

The following initial dosage is recommended:

Subcutaneous injections of 100 IU/kg twice daily or 100 IU/kg administered during 12 hours as continuous i.v. infusion.

Doses up to 120 IU/kg/12 hours do not give a significant accumulation of anti Xa activity.

As a rule parallel treatment with vitamin K antagonists should be started immediately. Treatment with FRAGMIN should be continued until the levels of the prothrombin complex factors (F II, F VII, F IX, F X) have decreased to a therapeutic level, usually for at least 5 days.

Extended treatment of symptomatic venous thromboembolism to reduce recurrence of VTE in patients with solid tumours

In patients with cancer and symptomatic venous thromboembolism, the recommended dosing of FRAGMIN is as follows.

Month 1

Administer FRAGMIN 200 IU/kg total body weight subcutaneously once daily for the first 30 days of treatment. The total daily dose should not exceed 18 000 IU. The table below lists the dose of FRAGMIN to be administered once daily during the first month for a range of patient weights.

Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during the First Month	
Body Weight (kg)	FRAGMIN Dose (IU) once daily
≤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 s.c. once daily during Months 2 through 6. The total daily dose should not exceed 18 000 IU. The table below lists the dose 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 (kg)	FRAGMIN Dose (IU) once daily
≤56	7 500
57 to 68	10 000
69 to 82	12 500
83 to 98	15 000
≥99	18 000

Recommended duration of treatment is 6 months (first month of FRAGMIN treatment is included). Relevance of continuing treatment beyond this period should be evaluated according to individual risk/benefit ratio, taking into account particularly the progression of cancer. No data is available with dalteparin beyond 6 months of treatment in the CLOT study.

Dose reductions for chemotherapy-induced thrombocytopenia in patients with cancer and acute symptomatic VTE

In patients receiving FRAGMIN who experience platelet counts between 50 000/ μ L and 100 000/ μ L, reduce the daily dose of FRAGMIN according to the dosage schedule in the table below until the platelet count recovers to \geq 100 000/ μ L. In patients receiving FRAGMIN who experience platelet counts $<$ 50 000/ μ L, FRAGMIN should be discontinued until the platelet count recovers above 50 000/ μ L.

Dose Reduction of FRAGMIN for Thrombocytopenia 50 000 – 100 000/μL			
Body Weight (kg)	Scheduled Dose (IU)	Reduced Dose (IU)	Mean Dose Reduction (%)
\leq 56	7 500	5 000	33
57 - 68	10 000	7 500	25
69 - 82	12 500	10 000	20
83 - 98	15 000	12 500	17
\geq 99	18 000	15 000	17

Dose reductions for renal insufficiency in extended treatment of acute symptomatic venous thromboembolism in patients with cancer

In patients with severely impaired renal function (creatinine clearance $<$ 30 mL/min), monitoring for anti-Xa levels is recommended to determine the appropriate FRAGMIN dose. Target anti-Xa range is 0.5 - 1.5 IU/mL. When monitoring anti-Xa in these patients, sampling should be performed 4 - 6 hrs after FRAGMIN dosing and only after the patient has received 3 - 4 doses.

Treatment of unstable coronary artery disease

120 IU/kg body weight is administered subcutaneously twice daily. Maximum dose is 10 000 IU/12 hours. Treatment should be continued for 6 days. There are insufficient data regarding the benefits from treatment beyond 6 days.

Concomitant therapy with low dose aspirin is recommended.

Anticoagulation for haemodialysis

Chronic renal failure - patients with no known bleeding risk:

- Haemodialysis for more than 4 hours: i.v. bolus injection of 30 – 40 IU/kg body weight followed by i.v. infusion of 10 – 15 IU/kg body weight per hour.
- Haemodialysis for a maximum of 4 hours: dose as above or only i.v. bolus injection of 5 000 IU.

Plasma level should be in the interval 0.5 - 1.0 IU anti-Xa/mL.

Acute renal failure - patients with high bleeding risk:

Intravenous bolus injection of 5 – 10 IU/kg body weight, followed by i.v. infusion of 4 – 5 IU/kg body weight per hour.

Plasma level should be in the interval 0.2 - 0.4 IU anti-Xa/mL.

Compatibility

FRAGMIN injection is compatible with isotonic sodium chloride and isotonic glucose infusions. Prepared infusion solution should be used within 12 hours.

Monitoring advice

FRAGMIN has an anticoagulant effect which may, for example, induce a certain elevation of Activated Partial Thromboplastin Time (APTT) and thrombin time. For laboratory monitoring of effect, however, anti-Xa methods based on chromogenic peptide substrate are to be recommended for measuring anti-Xa levels. Prolongation of APTT on haemodialysis and treatment of acute deep vein thrombosis should only be used as a criterion of overdose. Dose increases aiming at prolonging APTT may result in overdosing and haemorrhage. APTT or thrombin time should not be used because these tests are relatively insensitive to the activity of dalteparin.

Haemodialysis: New patients undergoing haemodialysis should be regularly checked with respect to anti-Xa levels during the first few weeks. As a rule, subsequent checks will be needed less frequently. Patients undergoing acute haemodialysis have a narrower therapeutic interval and should be subjected to comprehensive monitoring of anti-Xa levels.

Other Indications: Available data suggest that routine monitoring of anti-Xa levels is not required when FRAGMIN is used for indications other than haemodialysis, provided that the recommended dosages are not exceeded (see **DOSAGE AND ADMINISTRATION**). However, monitoring should be considered for the specific patient populations identified under PRECAUTIONS.

OVERDOSAGE

Doses of FRAGMIN exceeding the recommended dose may result in over-anticoagulation or bleeding. These may generally be stopped by the slow intravenous injection of protamine sulfate (1% solution), at a dose of 1.0 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 APPT 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 neutralised (maximum about 60 to 75%).

Protamine has an inhibiting effect on primary haemostasis and should only be used in an emergency. Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotension 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.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Solution for injection

Fixed single-dose syringes 2 500 IU anti-Xa/0.2 mL. Packs of 10s. Store below 30°C.

Fixed single-dose syringes 5 000 IU anti-Xa/0.2 mL. Packs 10s. Store below 30°C.

Graduated single-dose syringes 7 500 IU anti-Xa/0.75 mL. Packs of 10s. Store below 25°C.

Graduated single-dose syringes 10 000 IU anti-Xa/1 mL. Packs of 10s. Store below 25°C.

Fixed single-dose syringes 12 500 IU anti-Xa/0.5 mL. Packs of 5s. Store below 25°C.

Fixed single-dose syringes 15 000 IU anti-Xa/0.6 mL. Packs of 5s. Store below 25°C.

Fixed single-dose syringes 18 000 IU anti-Xa/0.72 mL. Packs of 5s. Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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S4 (Prescription Medicine)

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