NEW ZEALAND DATA SHEET

1. PRODUCT NAME

FRAGMIN® 10,000 IU/mL, 12,500 IU/mL, 25,000 IU/mL Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FRAGMIN solution for injection contains 10,000 IU/mL, 12,500 IU/mL, 25,000 IU/mL dalteparin sodium.

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 5,000 Da with 90% between 2,000 – 9,000 Da.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

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.

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 3,900, 2,940, 1,960 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 4,900, 5,880 and 7,060 IU anti-IIa respectively per syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of clotting in the extracorporeal system during haemodialysis and haemofiltration in connection with acute renal failure or chronic renal insufficiency.

Treatment of acute deep venous thrombosis (DVT) and pulmonary embolism (PE).

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.

Thromboprophylaxis in conjunction with surgery.

Prolonged thromboprophylaxis in orthopaedic surgery.

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

4.2 Dose and method of administration

PREVENTION OF CLOTTING DURING HAEMODIALYSIS AND HAEMOFILTRATION

Chronic Renal Failure, Patients with No Known Bleeding Risk:

Haemodialysis and haemofiltration for a maximum of 4 hours: Dose as below or only intravenous bolus injection of 5,000 IU.

Haemodialysis and haemofiltration for more than 4 hours: Intravenous bolus injection of 30-40 IU/kg body weight followed by intravenous infusion of 10-15 IU/kg body weight per hour. Administered doses normally produce a plasma level lying within the range of 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 intravenous infusion of 4-5 IU/kg body weight per hour. Plasma levels should lie within the range of 0.2-0.4 IU anti-Xa/mL.

TREATMENT OF ACUTE DEEP VENOUS THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE)

FRAGMIN can be administered subcutaneously (s.c.) either as a single daily injection or as twice daily injections.

Once daily administration: 200 IU/kg body weight is administered s.c. once daily. Monitoring of the anticoagulant effect is not necessary. The single daily dose should not exceed 18,000 IU.

Twice daily administration: A dose of 100 IU/kg body weight administered s.c. twice daily can be used for patients with increased risk of bleeding (thrombocytopenia and platelet defects, hypertensive or diabetic retinopathy, haemorrhagic diathesis, recent surgery, history of cerebral haemorrhage, malignant hypertension, severe liver and renal insufficiency).

Monitoring of the treatment is generally not necessary but can be performed with a functional anti-Xa assay. Maximum plasma levels are obtained 3-4 hours after s.c. injection when samples should be taken. Recommended plasma levels are between 0.5-1.0 IU anti-Xa/mL.

Simultaneous anticoagulation with oral vitamin-K antagonists can be started immediately. Treatment with FRAGMIN is continued until the prothrombin complex levels (factor II, VII, IX and X) have decreased to a therapeutic level. At least five days of combined treatment is normally required.

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

Dose Reduction of FRAGMIN for Thrombocytopenia 50,000 – 100,000/μL			
Body Weight (kg)	**Scheduled Dose (IU)**	**Reduced Dose (IU)**	**Mean Dose Reduction (%)**
≤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
≥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.

THROMBOPROPHYLAXIS IN CONJUNCTION WITH SURGERY

General Surgery with Associated Risk of Thromboembolic Complications

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 or longer.

General Surgery Associated with Additional Risk Factors and Orthopaedic Surgery

5,000 IU are given subcutaneously the evening before operation and 5,000 IU subcutaneously the following evenings. Treatment is continued until the patient is mobilised, in general 5-7 days or longer.

As an alternative 2,500 IU are given subcutaneously 1-2 hours before the operation and 2,500 IU subcutaneously 8-12 hours later. On the following days 5,000 IU subcutaneously each morning.

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

Prolonged Thromboprophylaxis in Orthopaedic Surgery (e.g. Hip Replacement surgery)

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

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

UNSTABLE CORONARY ARTERY DISEASE, i.e. UNSTABLE ANGINA AND NON-ST-ELEVATION MYOCARDIAL INFARCTION

120 IU/kg body weight is administered subcutaneously twice daily. Maximum dose is 10,000 IU/12 hours. Treatment should be continued for at least 6 days or longer if considered of benefit by the physician.

Concomitant therapy with low dose aspirin is recommended. In the clinical studies performed the dosages ranged between 75 to 325 mg in accordance with the local hospital routines.

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. Patients undergoing chronic

haemodialysis with FRAGMIN normally require only a few dose adjustments and therefore only a few checks 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 section 4.2). However, monitoring should be considered for the specific patient populations identified under section 4.4.

4.3 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.

Acute or sub-acute 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 section 4.4).

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.

4.4 Special warnings and precautions for use

Epidural or Spinal Anaesthesia

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 (see section 4.3).

Insertion or removal of the epidural or spinal catheter should be postponed to 10-12 hours after dalteparin doses administered for thrombosis prophylaxis, while in those receiving higher therapeutic dalteparin doses (such as 100 IU/kg -120 IU/kg every 12 hours or 200 IU/kg once daily), the interval should be a minimum of 24 hours. Extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurologic impairment such as back pain, sensory or motor deficits (numbness and weakness in lower limbs) and bowel or bladder dysfunction.

Interchangeability with Other Anticoagulants

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.

Intracranial Bleeding

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 section 4.6). 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/µL) 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 section 4.3).

In FRAGMIN clinical trials supporting non-cancer indications, platelet counts of <100,000/µL and <50,000/µL 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/µL occurred in 13.6% of patients, including 6.5% who also had platelet counts less than 50,000/µL. 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/µL.

Haemorrhage

As with all antithrombotic agents, there is a risk of systemic bleeding with FRAGMIN administration. 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. After treatment is initiated patients should be carefully monitored for bleeding complications. This may be done by regular physical examination of the patients, close observation of the surgical drain and periodic measurements of haemoglobin, and anti-Xa determinations.

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.

Allergic Reactions

The needle shield of Fragmin prefilled syringes may contain latex (natural rubber) which may cause severe allergic reactions in individuals with hypersensitivity to latex (natural rubber).

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 Population

There is limited experience of safety and efficacy in children. If dalteparin is used in these patients, anti-Xa levels should be monitored.

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.

4.5 Interaction with other medicines and other forms of interaction

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 vasodilatatory 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.

4.6 Fertility, pregnancy and lactation

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.

Caution is recommended when treating patients with an increased risk of haemorrhage, such as perinatal women (see section 4.4, Haemorrhage).

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.

Breast-feeding

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.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

- very common (≥1/10)
- common (≥1/100 to <1/10)
- uncommon (≥1/1,000 to <1/100)
- rare (≥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		
Unstable Angina and Non-ST-Elevation MI	**FRAGMIN** 120 IU/kg/12 hr s.c.[1] n (%)	**Heparin** i.v. and s.c.[2] n (%)	**Placebo** every 12 hr s.c. n (%)
Major Bleeding Events[3,4]	15/1497 (1.0)	7/731 (1.0)	4/760 (0.5)

[1] Treatment was administered for 5 to 8 days.

[2] Heparin i.v. infusion for at least 48 hours, APTT 1.5 to 2 times control, then 12,500 U s.c. every 12 hours for 5 to 8 days.

[3] Aspirin (75 to 165 mg per day) and beta blocker therapies were administered concurrently.

[4] Bleeding events were considered major if: 1) accompanied by a decrease in 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:

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

Bleeding Events Following Hip Replacement Surgery

	FRAGMIN vs Warfarin Sodium		**FRAGMIN vs Heparin**	
Indication	**Dosing Regimen**		**Dosing Regimen**	
Hip Replacement Surgery	**FRAGMIN[2]** 5,000 IU once daily s.c. n (%)	**Warfarin Sodium[1]** oral n (%)	**FRAGMIN[4]** 5,000 IU once daily s.c. n (%)	**Heparin** 5,000 IU three times a day s.c. 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 5,000 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 Population[1])

Study period	**FRAGMIN** **200 IU/kg (max 18,000 IU) s.c. once daily x 1 month, then 150 IU/kg (max. 18,000 IU) s.c. once daily x 5 months**			**OAC** **FRAGMIN 200 IU/kg (max 18,000 IU) s.c. once daily x 5-7 days and OAC for 6 months (target INR 2-3)**		
	Number at risk n	Patients with Major Bleeding n (%)	Patients with Any Bleeding n (%)	Number at risk n	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: Hypoaldosteronism.

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.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Signs and Symptoms

Doses of FRAGMIN exceeding the recommended dose may result in over-anticoagulation or bleeding.

Treatment of Overdosage

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

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.

Clinical Efficacy and Safety

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

	Dosing Regimen	
Indication	**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).

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No carcinogenicity tests have been performed with this agent.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride (Ph Eur.) is contained only in the 2,500 IU/0.2 mL, 7,500 IU/0.75 mL and 10,000 IU/1.0 mL syringes.

Water for Injections (Ph.Eur) is contained in all FRAGMIN products.

6.2 Incompatibilities

FRAGMIN solution for injection is compatible with isotonic sodium chloride (9 mg/mL) or isotonic glucose (50 mg/mL) infusion solution in glass bottles and plastic containers. Compatibility with FRAGMIN and other products has not been studied.

6.3 Shelf life

36 months

6.4 Special precautions for storage

FRAGMIN 2,500 IU/0.2 mL, 7,500 IU/0.3 mL, 10,000 IU/0.4 mL, and 5,000 IU/0.2 mL single dose syringes should be stored at or below 30°C. All other FRAGMIN products should be stored at or below 25°C.

6.5 Nature and contents of container

2,500 IU (anti-Xa) /0.2 mL, single dose syringes, 10 x 0.2 mL.

5,000 IU (anti-Xa) /0.2 mL, single dose syringes, 10 x 0.2 mL.

7,500 IU (anti-Xa) /0.3 mL, single dose syringes, 5 x 0.3 mL (not marketed).

10,000 IU (anti-Xa) /0.4 mL, single dose syringes, 5 x 0.4 mL (not marketed).

12,500 IU (anti-Xa) /0.5 mL, single dose syringes, 5 x 0.5 mL, 10 x 0.5 mL.

15,000 IU (anti-Xa) /0.6 mL, single dose syringes, 5 x 0.6 mL, 10 x 0.6 mL.

18,000 IU (anti-Xa) /0.72 mL, single dose syringes, 5 x 0.72 mL, 10 x 0.72 mL.

7,500IU (anti-Xa) /0.75 mL, graduated single dose syringes, 5 x 0.75 mL and 10 x 0.75 mL.

10,000IU (anti-Xa) /1.0 mL, graduated single dose syringes, 5 x 1.0 mL and 10 x 1.0mL.

Not all presentations are currently available in New Zealand.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

17 November 1998 (10,000 IU/mL)

17 December 1987 (12,500 IU/mL, 25,000 IU/mL)

10. DATE OF REVISION OF THE TEXT

25 March 2020

® Registered trademark.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Updated to include Latex Warning statement for prefilled syringes (both graduated and single dose) having needle shield cover.
4.4	Relocation of the “Paediatric Population”