AUSTRALIAN PRODUCT INFORMATION - FRAGMIN® INJECTION (DALTEPARIN SODIUM)

1. NAME OF THE MEDICINE

Dalteparin sodium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2,500 IU (anti-Xa) dalteparin sodium/0.2 mL injection syringe

5,000 IU (anti-Xa) dalteparin sodium/0.2 mL injection syringe

7,500 IU (anti-Xa) dalteparin sodium/0.75 mL injection syringe

10,000 IU (anti-Xa) dalteparin sodium/1 mL injection syringe

12,500 IU (anti-Xa) dalteparin sodium/0.5mL injection syringe

15,000 IU (anti-Xa) dalteparin sodium/0.6mL injection syringe

18,000 IU (anti-Xa) dalteparin sodium/0.72mL injection syringe

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.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection

A clear colourless or straw-coloured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 post-operative period of surgery.

4.2 Dose and method of administration

Do not administer FRAGMIN by the intramuscular route.

Thromboprophylaxis in Conjunction with Surgery

2,500 IU administered subcutaneously (s.c.) 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 post-operative 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 post-operative weeks.

Treatment of Acute Deep Vein Thrombosis

For patients with acute deep vein thrombosis FRAGMIN can be given either as a continuous intravenous (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. Table 1 below lists the dose of FRAGMIN to be administered once daily during the first month for a range of patient weights.

Table 1 - FRAGMIN Dose Administered During the First Month

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. Table 2 below lists the dose of FRAGMIN to be administered once daily for a range of patient weights during Months 2-6.

Table 2 - FRAGMIN Dose Administered 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 Table 3 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.

Table 3 - Dose Reduction of FRAGMIN for Thrombocytopenia (50,000–100,000/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.

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: A single bolus injection of 5,000 IU can be administered into the arterial side of the extracorporeal system, at the start of the procedure. The 5,000 IU starting dose for the single bolus dosing regimen can be adjusted, session-to-session, based on the outcome of the previous dialysis; the dose may be increased or decreased in steps of 500 or 1,000 IU until a satisfactory outcome is obtained (see section 5.1 Pharmacodynamic properties). If a dose of 10,000 IU or more will be required to achieve adequate anticoagulation, based on clinical assessment of clotting in the extracorporeal circuit, use with caution and consider performing an evaluation of the patient (including anti-Xa level) and the dialysis equipment before proceeding with the higher dose.

If anti-Xa levels are obtained during haemodialysis, expected levels are expected to be about 0.5 IU/mL during dialysis (2 hrs post-dosing) and 0.25 IU/mL at the end of dialysis (4 hrs post-dosing); however, dalteparin dose adjustments should generally be based on clinical assessment of clotting in the extracorporeal circuit along with access site compression time or other bleeding events (see section 5.1 Pharmacodynamic properties).

Alternatively, administer 30-40 IU/kg body weight intravenous bolus injection followed by 10-15 IU/kg body weight per hour intravenous infusion.

Acute Renal Failure - Patients with High Bleeding Risk:

Intravenous bolus injection of 5-0 IU/kg body weight, followed by i.v. infusion of 4-5 IU/kg body weight per hour.

Plasma anti-Xa level should be in the interval 0.2-0.4 IU/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. However, monitoring should be considered for the specific patient populations identified under section 4.4 Special warnings and precautions for use.

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 Special warnings and precautions for use).

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 Contraindications).

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, physicochemical, 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 Fertility, pregnancy and lactation - 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/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 Contraindications).

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.

The concomitant use with drugs affecting haemostasis, such as thrombolytic agents, other anticoagulants, NSAIDs, platelet inhibitors, or dextran may enhance the anticoagulant effect of dalteparin and is not recommended. Appropriate caution should be exercised under specific circumstances of switching anticoagulant therapy (see section 4.5 Interactions with other medicines and other forms of interactions).

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 post-operative 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 during maintenance treatment 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 re-thrombosis.

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

Allergic Reactions

<u>For labels with the prefilled syringes (fixed dose and graduated syringes)</u>

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 Use

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

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 Interactions with other medicines and other forms of interactions

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

1. **Drugs Increasing Effects of Dalteparin**

Enhancement of anticoagulant effect by thrombolytic agents, aspirin and other NSAIDs with effects on platelets, other anticoagulants, 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 (see section 4.4 Special warnings and precautions for use - Haemorrhage).

2. **Drugs Antagonising Effects of Dalteparin**

Reduction of anticoagulant effect by antihistamines, digitalis glycosides, tetracycline and ascorbic acid. The concomitant use of dalteparin with andexanet alfa may reduce the effectiveness of dalteparin. Andexanet alfa, a recombinant modified human coagulation factor Xa used for reversal of anticoagulation with apixaban or rivaroxaban, has been shown to bind to heparin-bound anti-thrombin III (ATIII) and may reduce the anticoagulant effect of dalteparin.

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.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

No data available.

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.

Caution is recommended when treating patients with an increased risk of haemorrhage, such as perinatal women (see section 4.4 Special warnings and precautions for use - 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.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

In table 4 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.

Table 4 - Adverse Events Associated with Dalteparin Therapy in Patients Participating in Controlled Clinical Studies

MedDRA System Organ Class	Frequency	Adverse Event
Blood and Lymphatic System Disorders	Common Rare	Reversible non-immunologically-mediated thrombocytopenia (type I) Immunologically-mediated heparin-induced thrombocytopenia (type II, with or without associated thrombotic complications – arterial and/or thrombosis or thromboembolism)
Immune System Disorders	Uncommon Rare	Allergic reactions 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 Rare	Rash, urticaria, pruritus Bullous eruptions, skin necrosis, alopecia
Musculoskeletal and Connective Tissue Disorders	Uncommon	Osteoporosis
General Disorders and Administration Site Conditions	Uncommon Common	Pain at injection site Haematoma at injection site

Unstable Angina and Non-ST-Elevation Myocardial Infarction

Table 5 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.

Table 5 - 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]	**Heparin** i.v. and s.c.[2]	**Placebo** 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

Table 6 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.

Table 6 - 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

Table 7 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.

Table 7 - 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	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.

***Metabolic and Nutrition Disorders*:** Hyperkalaemia.

***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 Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/safety/reporting-problems.

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 IU of FRAGMIN given. A second infusion of 0.5 mg protamine sulfate per 100 IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. Even with these additional doses of protamine, the APTT may remain more prolonged than would usually be

found following administration of conventional heparin. In all cases, the anti-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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 anti-thrombotically 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 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 8 below).

Table 8 - 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 post-operatively 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 9 below). The benefit was maintained over the 6-month study period.

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

Table 9 - Recurrent VTE in Patients with Cancer (Intention to Treat population)[1]

Study Period	**FRAGMIN arm**			**OAC arm**		
	FRAGMIN 200 IU/kg (max. 18,000 IU) s.c. once daily x 1 month, then 150 IU/kg (max. 18,000 IU) s.c. once daily x 5 months			FRAGMIN 200 IU/kg (max 18,000 IU) s.c. once daily x 5-7 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).

Parrot Study (A6301091)

A phase IIIb open-label study in adults aged 18 to 85 years that allowed flexible dosing with increment/decrement of 500 or 1,000 IU following standard dalteparin sodium 5,000 IU bolus

to optimise treatment for the prevention of clotting within the extracorporeal system during haemodialysis procedures for subjects with chronic renal insufficiency.

Subjects had been previously treated with UFH or LMWH and had end-stage renal failure requiring 3 or 4 haemodialysis (HD) sessions each of 4 hours or less per week.

Table 10- Study Demographics and Trial Design

Diagnosis	**Dalteparin dosage, route of administration and duration**	**Study subjects**
Subjects with end stage renal failure requiring 3 or 4 HD sessions (for 4 hours or less) per week, with no other known risks of bleeding.	5,000 IU single bolus dose given into the arterial side of the dialyser at the start of the procedure. This dose could be adjusted by increment/decrement of 500 IU or 1,000 IU, at the discretion of the investigator. Criteria for dose adjustments were occurrence of clotting grade 3 or 4, minor bleeding during HD or between HD sessions, prolonged access compression time (>10 minutes) or other clinical events. Study duration for a maximum of 20 HD sessions	152 subjects enrolled and treated Gender: 106 males, 46 females

The mean proportion of successful HD sessions (defined as a HD session which was completed as planned, without the need for premature termination due to clotting in the HD circuit) was 99.9% (2,774 of 2,776 evaluable HD sessions; 50 HD sessions were excluded from the analysis because the effect of dalteparin sodium could not be assessed), with a 95% CI of 99.7% to 100.0%. No HD session was prematurely terminated due to a safety event of bleeding.

For subjects who completed at least one HD session, the dalteparin dose was adjusted for 79 (52.3%) subjects, and 72 (47.7%) subjects received the standard fixed dose of 5,000 IU per HD session at all HD sessions.

The mean FRAGMIN dose was 5,488 IU and the median FRAGMIN dose was 5,000 IU. Very few subjects received a dose over 10,000 IU. There was no evidence of bioaccumulation of anti-Xa serum levels. Only for 2 subjects, the pre-HD session value was above the threshold of <0.4 IU/mL at HD 10 but this was resolved at HD session 20. For each HD session, the anti-Xa serum levels at 2 hours post analysis increased from pre- HD session, before starting to decrease at 4 hours post-HD session.

Within the limitations of a single-arm, open label study, the results demonstrate that a flexible dosing regimen of dalteparin sodium administered into the arterial side of the extracorporeal system during HD sessions up to 4 hours in subjects with chronic renal failure and no other known risks of bleeding is effective and well tolerated, and that a flexible dosing regimen is appropriate to address the potential limitations of the fixed dose regimen (5,000 IU).

5.2 Pharmacokinetic properties

Absorption

Bioavailability is approximately 90% after subcutaneous injection.

Elimination

Half-life after intravenous injection is two hours and after subcutaneous injection is 3-4 hours. 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 q.s. (in the 2,500 IU anti-Xa/0.2 mL, 7,500 IU anti-Xa/0.75 mL and 10,000 IU anti-Xa/1 mL syringe presentations only).
- Water for Injections.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Fixed single-dose syringes 2,500 IU & 5,000 IU anti-Xa/0.2 mL: Store below 30°C.

Graduated single-dose syringes 7,500 IU anti-Xa/0.75 mL & 10,000 IU anti-Xa/1 mL: Store below 25°C.

Fixed single-dose syringes 12,500 IU anti-Xa/0.5 mL, 15,000 IU anti-Xa/0.6 mL & 18,000 IU anti-Xa/0.72 mL: Store below 25°C.

6.5 Nature and contents of container

Fixed single-dose syringes 2,500 IU anti-Xa/0.2 mL. Packs of 5s[#], 10s.

Fixed single-dose syringes 5,000 IU anti-Xa/0.2 mL. Packs of 5s[#], 10s, 15s[#].

Graduated single-dose syringes 7,500 IU anti-Xa/0.75 mL. Packs of 2s[#], 5s[#], 6s[#], 10s[#], 15s[#].

Graduated single-dose syringes 10,000 IU anti-Xa/1 mL. Packs of 2s[#], 5s[#], 6s[#], 10s, 15s[#].

Fixed single-dose syringes 12,500 IU anti-Xa/0.5 mL. Packs of 2s[#], 5s[#], 10s.

Fixed single-dose syringes 15,000 IU anti-Xa/0.6 mL. Packs of 2s[#], 5s[#] ,10s.

Fixed single-dose syringes 18,000 IU anti-Xa/0.72 mL. Packs of 2s[#], 5s[#], 10s.

To assist with preventing needle stick injuries, the single-dose syringes are available with a Needle-Trap feature[#] (needle catcher), which forms part of the syringe label attached directly to the glass barrel of the syringe.

Not currently marketed in Australia.

6.6 Special precautions for disposal

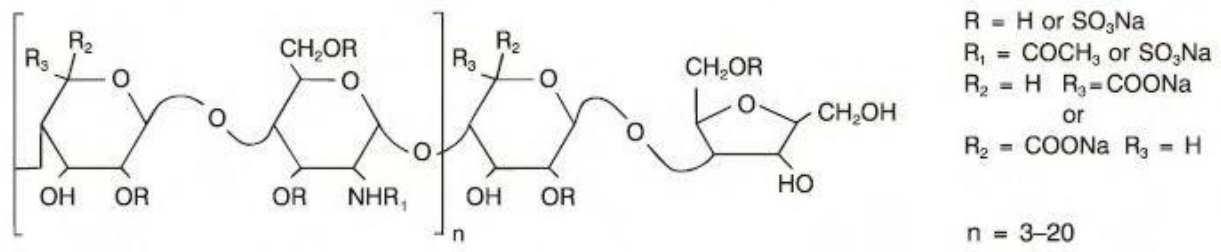
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

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.

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.

Chemical structure



CAS number

9041-08-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000

Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

05 October 2022
2,500 IU anti-Xa/0.2 mL; 5,000 IU anti-Xa/0.2 mL
12,500 IU anti-Xa/0.5 mL; 15,000 IU anti-Xa/0.6 mL; 18,000 IU anti-Xa/0.72 mL
7,500 IU anti-Xa/0.75 mL; 10,000 IU anti-Xa/1 mL

10. DATE OF REVISION

03 July 2025

® Registered trademark

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Throughout	Minor editorial and typographical corrections
4.5	Update the drug interaction section to include the interaction with andexanet alfa
4.4 & 4.5	Change from “oral anticoagulants” to “other anticoagulants”