Dalteparin Sodium Injection

FRAGMIN®

1. NAME OF MEDICINAL PRODUCT

FRAGMIN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Dalteparin Sodium Ph.Eur.

1 single dose syringe 2500 IU (anti-Factor Xa)/0.2 ml, 5000 IU (anti-Factor Xa)/0.2 ml, 7500 IU (anti-Factor Xa)/0.3 ml and 1 single dose graduated syringe 10000 IU (anti-Factor Xa)/1 ml.
Multi-dose vial of 10000 IU (anti-Factor Xa)/ml, in 10 ml

Potency is described in anti-Factor Xa international units (IU) of the 1st International Standard for Low Molecular Mass Heparin.

For the full list of excipients, see section 6.1.

All strengths/presentations mentioned in this document might not be available in the market.

3. PHARMACEUTICAL FORM

Sterile solution for subcutaneous and intravenous administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Treatment of acute deep-vein thrombosis.

2. Prevention of clotting in the extra corporeal system during haemodialysis and haemofiltration in patients with acute renal failure or chronic renal insufficiency.

3. Thromboprophylaxis in conjunction with surgery.

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4. For prophylaxis of deep-vein thrombosis, in patients who are at risk of thromboembolic complications due to severely restricted mobility during acute illness.

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

6. For the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer.

4.2 Posology and Method of Administration

See section 4.4 **Special Warnings and Special Precautions for Use**

General - DO NOT ADMINISTER DALTEPARIN BY THE INTRAMUSCULAR ROUTE.

Compatibility with IV Solutions - Dalteparin is compatible with isotonic sodium chloride (9 mg/ml) or isotonic glucose (50 mg/ml) infusion solution in glass bottles and plastic containers.

1. <u>Treatment of Acute Deep-vein Thrombosis</u>
Administer dalteparin subcutaneously (SC) either as a single daily injection or as two daily injections. Simultaneous anticoagulation with oral vitamin-K antagonists can be started immediately. Continue combined treatment until the prothrombin complex tests have reached therapeutic levels (usually at least 5 days). Outpatient treatment is feasible using the same doses recommended for treatment in a medical institution.

- **Once daily administration** - 200 IU/kg total body weight SC once daily, up to a maximum of 18,000 IU. Monitoring of the anticoagulant effect is not necessary.

- **Twice daily administration** - Alternatively, a dose of 100 IU/kg total body weight administered SC twice daily may be given. Monitoring of the anticoagulant effect is generally not necessary but should be considered for specific patient populations (see section 4.4 **Special Warnings and Special Precautions for Use**). Samples should be taken during maximum plasma levels (3 to 4 hours after a SC injection). Recommended peak plasma levels are between 0.5 and 1.0 IU anti-Factor Xa/ml.

2. <u>Prevention of Clotting in the Extra-corporeal System during Haemodialysis and Haemofiltration</u>
Administer dalteparin intravenously (IV), selecting the appropriate regimen from those described below.

- **Patients with chronic renal insufficiency or patients with no known risk of Bleeding** - These patients normally require few dose adjustments, and therefore, frequent monitoring of anti-Factor Xa levels is not necessary for most patients.

Recommended doses usually produce plasma levels between 0.5 to 1.0 IU anti-Factor Xa/ml during dialysis.

- **Haemodialysis and haemofiltration for a maximum of 4 hours** - Either 30 to 40 IU/kg total body weight IV bolus injection followed by 10 to 15 IU/kg/hour IV infusion, or a single IV bolus injection of 5000 IU.

- **Haemodialysis and haemofiltration for more than 4 hours** - 30 to 40 IU/kg total body weight IV bolus injection, followed by 10 to 15 IU/kg/hour IV infusion.

- **Patients with acute renal failure, or patients with a high risk of bleeding -** Administer 5 to 10 IU/kg total body weight as IV bolus injection, followed by 4 to 5 IU/kg/hour IV infusion. Patients undergoing acute haemodialysis have a narrower therapeutic range than patients on chronic haemodialysis, and should undergo comprehensive monitoring of anti-Factor Xa levels. Recommended plasma levels are between 0.2 and 0.4 IU anti-Factor Xa/ml.

3. <u>Thromboprophylaxis in Conjunction with Surgery</u>

Administer dalteparin subcutaneously (SC). Monitoring of the anticoagulant effect is generally not necessary. If done, samples should be taken during maximum plasma levels (3 to 4 hours after an SC injection). Recommended doses usually produce peak plasma levels between 0.1 and 0.4 IU anti-Factor Xa/ml.

- **General surgery**
  Select the appropriate regimen from those listed below.

- **Patients at risk for thromboembolic complications** – 2500 IU SC within 2 hours before surgery and 2500 IU SC each post-operative morning until the patient is mobilized (generally 5 to 7 days or longer).

- **Patients with additional risk factors for thromboembolism** (e.g., malignancy) - Administer dalteparin until the patient is mobilized (generally 5 to 7 days or longer).

    - **Start on day before surgery**: 5000 IU SC on the evening before surgery. Following surgery, 5000 IU SC each evening.

    - **Start on day of surgery**: 2500 IU SC within 2 hours before surgery and 2500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each morning.

- **Orthopaedic surgery (such as hip replacement surgery) -** Administer dalteparin for up to 5 weeks after surgery, selecting one of the regimens listed below.

    - **Preoperative start - Evening before surgery**: 5000 IU SC on the evening before surgery. Following surgery, 5000 IU SC each evening.

- **Preoperative start - Day of surgery**: 2500 IU SC within 2 hours before surgery and 2500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each morning.

- **Post-operative start**: 2500 IU SC 4 to 8 hours after surgery, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each day.

4. For Prophylaxis of Deep Vein Thrombosis, in Patients who are at Risk of Thromboembolic Complications due to Severely Restricted Mobility During Acute Illness

Administer 5000 IU of dalteparin subcutaneously (SC) once daily, generally for 12 to 14 days or longer in patients with continued restricted mobility. Monitoring of the anticoagulant effect is generally not necessary.

5. Unstable Coronary Artery Disease (Unstable Angina and Non-ST-elevation Myocardial Infarction)

Administer dalteparin 120 IU/kg total body weight subcutaneously (SC) every 12 hours up to a maximum dose of 10,000 IU/12 hours. Unless specifically contraindicated, patients should also receive concomitant therapy with acetylsalicylic acid (75 to 325 mg/day).

Continue treatment until the patient is clinically stable (generally at least 6 days), or longer if considered of benefit by the physician. Thereafter, extended treatment with a fixed dose of dalteparin is recommended until a revascularization procedure is performed (such as percutaneous interventions [PCI] or coronary artery bypass graft [CABG]). The total treatment period should not exceed 45 days. The dose of dalteparin is selected according to the patient's gender and weight:

- For women weighing less than 80 kg and men weighing less than 70 kg, administer 5000 IU SC every 12 hours.
- For women weighing at least 80 kg and men weighing at least 70 kg, administer 7500 IU SC every 12 hours.

Monitoring of the anticoagulant effect is generally not necessary but should be considered for specific patient populations (see section 4.4 **Special Warnings and Special Precautions for Use**). Samples should be taken during maximum plasma levels (3 to 4 hours after a SC injection). Recommended peak plasma levels are between 0.5 and 1.0 IU anti-Factor Xa/ml.

6. Extended Treatment of Symptomatic Venous Thromboembolism in Patients with Cancer

In patients with cancer and symptomatic venous thromboembolism, the recommended dosing of FRAGMIN is as follows: for the first 30 days of treatment administer FRAGMIN 200 IU/kg total body weight subcutaneously (S.C.) once daily. The total daily dose should not exceed 18,000 IU. Table 1 lists the dose of FRAGMIN to be administered once daily during the first month for a range of patient weights.

Month 1

Table 1 Dose of FRAGMIN to be Administered Subcutaneously by Patient Weight during the First Month		
Body Weight (lbs)	**Body Weight (kg)**	**FRAGMIN Dose (IU) (prefilled syringe) once daily**
≤124	≤56	10,000
125 to 150	57 to 68	12,500
151 to 181	69 to 82	15,000
182 to 216	83 to 98	18,000
≥217	≥99	18,000

Months 2 to 6

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

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

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

Safety and efficacy beyond 6 months have not been evaluated in patients with cancer and acute symptomatic VTE (see section 4.4 **Special Warnings and Special Precautions for Use, Thrombocytopenia**).

Dose reductions for thrombocytopenia in patients with cancer and acute symptomatic VTE - In patients receiving FRAGMIN who experience platelet counts between 50,000 and 100,000/mm^3, reduce the daily dose of FRAGMIN by 2,500 IU until the platelet count recovers to ≥100,000/mm^3. In patients receiving FRAGMIN who experience platelet counts <50,000/mm^3, FRAGMIN should be discontinued until the platelet count recovers above 50,000/mm^3.

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

In patients with severely impaired renal function (CrCl <30 ml/min), monitoring for anti-Factor Xa levels is recommended to determine the appropriate FRAGMIN dose. Target anti-

Factor Xa is 0.5-1.5 IU/ml. When monitoring anti-Factor Xa in these patients, sampling should be performed 4-6 hrs after FRAGMIN dosing and only after the patient has received 3-4 doses.

4.3 Contraindications

Dalteparin should not be used in patients who have the following:

- Established or suspected history of immunologically-mediated heparin-induced thrombocytopenia (type II),
- Active, clinically-significant bleeding (such as gastrointestinal ulceration or bleeding, or cerebral hemorrhage),
- Serious coagulation disorders,
- Septic endocarditis,
- Injuries to and operations in the central nervous system, eyes and/or ears.
- Hypersensitivity to Dalteparin, or other low-molecular weight heparins, or heparins, or pork products.

Because of an increased risk of bleeding, high doses of dalteparin (such as those needed to treat acute deep-vein thrombosis, pulmonary embolism, and unstable coronary artery disease) should not be used in patients who will receive spinal or epidural anesthesia or other procedures requiring spinal puncture (see section 4.4 **Special Warnings and Precautions for Use**).

FRAGMIN presentations containing benzyl alcohol (FRAGMIN 10,000 IU (anti-Factor Xa)/ml 10 ml vial and FRAGMIN 25,000 IU (anti-Factor Xa)/ml 4 ml vial) must not be given to pre-mature babies or neonates. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.4 Special Warnings and Special Precautions for Use

FRAGMIN should not be administered intramuscularly. Due to the risk of hematoma, intramuscular injection of other medical preparations should be avoided when the twenty-four hour dose of dalteparin sodium exceeds 5,000 IU.

Epidural or Spinal Anesthesia

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low-molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in neurological lesions of different degrees, including 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 (spinal cord decompression) is necessary (see section 4.3 **Contraindications**).

In order to reduce the risk of bleeding associated with the use of FRAGMIN during spinal or epidural anaesthesia, it is preferable to insert or remove the catheter when the anticoagulant effect of FRAGMIN is at its lowest level. Insertion or removal of a catheter should be postponed for 12 hours after the administration of the last dose of FRAGMIN for the prophylaxis of deep-vein thrombosis. This delay should be 24 hours in patients with increased risk of haemorrhage. All epidural/spinal anaesthesia or spinal puncture in combination with curative treatment of deep-vein thrombosis is contra-indicated (see sections 4.2. **Posology and Method of Administration** and 4.3. **Contraindications**). After removal of the catheter, it is necessary to wait for at least 4 hours before the next administration of FRAGMIN.

When the physician decides to administer an anticoagulant prior to an epidural/spinal anaesthesia or spinal puncture, extreme caution and frequent monitoring is required in order to detect any sign or symptom of a neurological manifestation, such as dorsal pain, sensory or motor disorder (numbness or weakness in the lower limbs, bladder dysfunction). Nursing staff should be trained specifically in early recognition of symptoms of a neurological manifestation. Patients should be asked to inform their physician when symptoms of a neurological disorder appear.

When signs or symptoms of an intraspinal hematoma are suspected, urgent diagnosis and treatment, including spinal cord decompression, are required.

Risk of Hemorrhage

Dalteparin should be used with caution in patients who have a potentially higher risk of hemorrhage, such as patients with thrombocytopenia, platelet disorders, severe liver or kidney insufficiency, uncontrolled hypertension, or hypertensive or diabetic retinopathy and known hypersensitivity to heparin preparations and/or low-molecular weight heparin preparations. 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 and other conditions with suspicion of increased risk of haemorrhage.

Thrombocytopenia

Due to the risk of thrombocytopenia, it is recommended that the platelets be counted before the initiation of dalteparin treatment and be followed regularly during treatment. Special caution is necessary if thrombocytopenia arises rapidly or to a significant degree (less than 100,000/μL or mm^3) during treatment with Dalteparin. In either case, an *in vitro* test for antiplatelet antibodies in the presence of heparins or low-molecular weight heparins is recommended. If the result of the *in vitro* test is positive or inconclusive, or no test is performed, treatment with dalteparin should be stopped (see section 4.3 **Contraindications**). Treatment should then be started with a fractionated heparin that did not cause aggregation with the platelets of the patient in an *in-vitro* aggregation test. Subsequently, platelet count should be performed at least twice a week, in particular during the first 3 weeks.

Important: heparin-induced type II thrombocytopenia should not be confused with early post-operative thrombocytopenia.

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

Monitoring anti-Factor Xa Levels

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

The time needed for clot formation measured as (Activated Partial Thromboplastin Time (APTT) is only prolonged to a moderate extent by dalteparin, and should not be used because these tests are relatively insensitive to the activity of Dalteparin. Increase of dose with the aim to prolong APTT therefore be a risk of overdose and haemorrhage. For laboratory monitoring of haemorrhagic risk, functional anti-Factor Xa methods are recommended.

Hyperkalemia

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. The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.

Haemodialysis

Patients under chronic haemodialysis with dalteparin need as a rule fewer dosage adjustments and as a result fewer controls of anti-Factor Xa levels. Patients undergoing acute haemodialysis may be more unstable and should have a more comprehensive monitoring of anti-Factor Xa levels.

Interchangeability With Other Anticoagulants

The biological activity of different low-molecular weight heparins, unfractionated heparin or synthetic polysaccharides cannot be expressed in a test which admits simple dose comparison between different preparations. Since the specific low-molecular weight heparin preparations have diverse characteristics, dose adjustment is necessary. Therefore, particular caution is required and the recommended instructions for the use of each specific product should be respected.

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

Osteoporosis

Long-term treatment with heparin has been associated with a risk of osteoporosis. Although this has not been observed with dalteparin the risk of osteoporosis cannot be excluded.

Pregnancy

The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, [Dalteparin] multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed.

Pediatric Patients

There is limited safety and efficacy information on the use of dalteparin in pediatric patients. If dalteparin is used in these patients, anti-Factor Xa levels should be monitored.

The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, [dalteparin] multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see section 4.6 **Fertility**, **Pregnancy and Lactation**).

Geriatric Use

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.

Of the total number of patients in clinical studies of FRAGMIN, 5204 patients were 65 years of age or older and 2123 were 75 or older. No overall differences in effectiveness were observed between these subjects and younger subjects. Some studies suggest that the risk of bleeding increases with age. Post-marketing surveillance and literature reports have not revealed additional differences in the safety of FRAGMIN between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised, particularly in geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function (see sections **Pharmacodynamic Properties Pharmacokinetic Properties** under **Pharmacological Properties**).

Drug/Laboratory Test Interactions

Elevations of Serum Transaminases

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.

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).

4.5 Interaction with Other Medicaments and Other Forms of Interaction

Simultaneous use of drugs affecting the hemostatic functions, such as anti-platelet agents, thrombolytic agents, acetyl salicylic acid,, NSAIDs, GP IIb/IIIa receptor antagonists, vitamin-K antagonists and dextran, may intensify the anticoagulant effect of dalteparin (see section 4.2 **Posology and Method of Administration - Unstable Coronary Artery Disease (Unstable Angina and Non-ST-elevation Myocardial Infarction)**.

Because NSAIDs and ASA 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 ASA in patients with renal failure.

As heparin has been shown to interact with following drugs: intravenous nitroglycerine, high dose penicillin, sulfinpyrazone, probenecid, etacrynic acid, cytostatic agents, quinine, antihistamines, digitalis, tetracyclines, and also with tobacco smoking and ascorbic acid. Interaction with these substances cannot be ruled out for dalteparin.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Experience so far does not reveal any evidence of an impairment to the embryo or foetus by means of low molecular treatment of the mother. Only very limited controlled studies are so far available on the use of low-molecular heparins in pregnancy. Dalteparin does not pass the placenta.

Epidural anaesthesia during childbirth is absolutely contraindicated in women who are being treated with high-dose anticoagulants (see section 4.3 **Contraindications**). In pregnant women during the last trimester, dalteparin anti-Factor Xa half-lives of 4 to 5 hours were measured.

Animal experiments did not show any teratogenic or fetotoxic properties of dalteparin (see section 5.3 **Preclinical safety data**).

FRAGMIN 10,000 IU/ml (10 ml vial) and FRAGMIN 25,000 IU/ml (4 ml vial), solution for

injection, contain benzyl alcohol as a preservative. As benzyl alcohol may cross the placenta, FRAGMIN without preservative should therefore be used during pregnancy (see section 4.4 **Special Warnings and Special Precautions for Use**).

Medications containing benzyl alcohol - (see section 4.4 **Special Warnings and Special Precautions for Use- Pediatric Patients)**

Lactation
Small amounts of dalteparin sodium pass into breast milk. So far, studies revealed anti-factor Xa levels of 2% to 8% of the plasma levels in breast milk (15 women, 3rd to 5th day of lactation, 2 to 3 hours after SC administration of dalteparin). An anticoagulant effect on the infant appears unlikely, however dalteparin should be administered in lactation only when the benefits of the treatment for the mother outweigh the potential risks to the infant.

4.7 Effects on Ability to Drive and Use Machines

FRAGMIN does not influence the ability to drive a car or to operate machinery.

4.8 Undesirable Effects

About 3% of the patients having had prophylactic treatment reported side-effects.

The reported adverse reactions, which may possibly be associated to dalteparin sodium, are listed in the following table by system organ class and frequency group: *common* (≥1/100, <1/10), *uncommon* (≥1/1000, <1/100), *rare* (≥1/10,000, <1/1000).

System Organ Class	*Frequency*	*Adverse Reactions*
Blood and lymphatic system disorders	Common	Mild thrombocytopenia (type I), which usually is reversible during the treatment. Haemorrhage
Hepatic and biliary disorders	Common	Transient elevation of transaminases
Skin and subcutaneous tissue disorders	Rare	Skin Necrosis, transient alopecia
General disorders and administration site conditions	Common	Subcutaneous hematoma at the injection site. Pain at the injection site.
	Rare	Allergic reaction

In post-marketing experience, the following additional undesirable effects have been reported:

- *Blood and Lymphatic System Disorders:* immunologically-mediated heparin-induced thrombocytopenia (type II, with or without associated thrombotic complications),
- *Immune System Disorders:* anaphylactic reactions,

- *Nervous System Disorders:* intracranial bleeds have been reported and some have been fatal,
- *Vascular Disorders:* haemorrhage (bleeding at any site), some cases reported have been fatal,
- *Gastrointestinal Disorders:* retroperitoneal bleeds have been reported and some have been fatal,
- *Skin and Subcutaneous Tissue Disorders:* skin necrosis, rash,
- *Injury, Poisoning and Procedural Complications:* spinal or epidural hematoma.

The risk of bleeding is depending on dose. Most bleedings are mild. Severe bleedings have been reported, some cases with fatal outcome.

Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium.

Rarely, clinically significant hyperkalaemia may occur particularly in patients with chronic renal failure and diabetes mellitus (see section 4.4 **Special Warnings and Special Precautions for Use**).

Long-term treatment with heparin has been associated with a risk of osteoporosis. Although this has not been observed with dalteparin, the risk of osteoporosis cannot be excluded.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. The safety of long-term dalteparin administration has not been established.

4.9 Overdose

The anticoagulant effect induced by dalteparin can be inhibited by protamine (1 mg). Protamine neutralises the prolongation of the coagulation time induced by 100 anti-Factor Xa units of dalteparin, while the anti-Factor Xa activity is neutralised to about 25%-50%. Protamine has in itself an inhibiting effect on the primary hemostasis and shall only be used in emergency cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antithrombotics. ATC code: B01AB04.

FRAGMIN is an antithrombotic drug containing dalteparin sodium. Dalteparin is a low-molecular weight heparin derived from porcine intestinal mucosa, with an average molecular weight of 6,000 Daltons (range between 5600 and 6400 Daltons). The antithrombotic effect of dalteparin sodium is due to its property to enhance the inhibition of Factor Xa and thrombin by antithrombin. In man, dalteparin potentiates preferentially the

inhibition of coagulation Factor Xa, while only slightly affecting clotting time, e.g., activated partial thromboplastin time (APTT).

Dalteparin sodium has less effect on platelet activation and platelet adhesion compared to heparin; it has consequently a limited effect on primary haemostasis. However, some of the antithrombotic properties of dalteparin sodium are considered to be based on its effect on the blood vessel wall or on the fibrinolytic system.

Clinical efficacy and safety
In a large international randomized, controlled multi-center study, entitled PROTECT (PROphylaxis for ThromboEmbolism in Critical Care Trial), the thromboprophylactic effect of dalteparin 5,000 IU once daily was compared to unfractionated heparin (UFH) 5,000 IU twice daily in 3746 critically ill medical (76%) and surgical patients who were admitted in the intensive care unit (ICU) for at least 3 days. The primary outcome was proximal leg deep vein thrombosis (DVT) as determined by periodic compression ultrasound. Approximately 90% of the patients required mechanical ventilation. Treatment with the study drug was allowed for the duration of ICU stay to a maximum of 90 days. The median duration of study drug in both groups was 7 days (interquartile range, 4 to 12). A blinded adjudication of thrombotic and bleeding events was performed.

There was no significant difference in proximal leg DVT between the two groups (5.1% in the dalteparin group and 5.8% in the UFH group, hazard ratio 0.92; 95% CI, 0.68 to 1.23; P=0.57).

A significant 49% risk reduction in the secondary end-point of pulmonary embolism (PE) was seen with dalteparin (absolute difference 1.0%; 95% CI 0.30 to 0.88; P=0.01).

There was no significant differences between the two groups in the rates of major bleeding (hazard ratio, 1.00; 95% CI, 0.75 to 1.34; P = 0.98) or death in the hospital (hazard ratio, 0.92; 95% CI, 0.80 to 1.05; P = 0.21).

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

Clinical trials:

Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction
In a double-blind, randomized, placebo-controlled clinical trial, patients who recently experienced unstable angina with EKG changes or non-Q-wave myocardial infarction (MI) were randomized to FRAGMIN Injection 120 IU/kg every 12 hours subcutaneously (SC) or

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

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

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

Abdominal surgery patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes, or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism. FRAGMIN administered once daily SC beginning prior to surgery and continuing for 5 to 10 days after surgery, was shown to reduce the risk of DVT in patients at risk for thromboembolic complications in two double-blind, randomized, controlled clinical trials performed in patients undergoing major abdominal surgery. In the first study, a total of 204 patients were enrolled and treated; 102 received FRAGMIN and 102 received placebo. The mean age of the study population was 64 years (range 40 to 98 years) and the majority of patients were female (54.9%). In the second study, a total of 391 patients were enrolled and treated; 195 received FRAGMIN and 196 received heparin. The mean age of the study population was 59 years (range 30 to 88 years) and the majority of patients were female (51.9%). FRAGMIN 2500 IU was found to be superior to placebo and similar to heparin in reducing the risk of DVT.

Prophylaxis of Deep Vein Thrombosis in Patients Following Hip Replacement Surgery

In an open-label randomized study, FRAGMIN 5000 IU administered once daily SC was compared with warfarin sodium, administered orally, in patients undergoing hip replacement surgery. Treatment with FRAGMIN was initiated with a 2500 IU dose SC within 2 hours before surgery, followed by a 2500 IU dose SC the evening of the day of surgery. Then, a

dosing regimen of FRAGMIN 5000 IU SC once daily was initiated on the first post-operative day. The first dose of warfarin sodium was given the evening before surgery, then continued daily at a dose adjusted for INR 2.0 to 3.0. Treatment in both groups was then continued for 5 to 9 days post-operatively. Of the total enrolled study population of 580 patients, 553 were treated and 550 underwent surgery. Of those who underwent surgery, 271 received FRAGMIN and 279 received warfarin sodium. The mean age of the study population was 63 years (range 20 to 92 years) and the majority of patients were white (91.1%) and female (52.9%). The incidence of deep vein thrombosis (DVT), any vein, as determined by evaluable venography, was significantly lower for the group treated with FRAGMIN compared with patients treated with warfarin sodium (28/192 vs 49/190; p = 0.006)

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

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

Patients with Cancer and Acute Symptomatic Venous Thromboembolism

In a prospective, multi-center, open-label, clinical trial, 676 patients with cancer and newly diagnosed, objectively confirmed acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were studied. Patients were randomized to either FRAGMIN 200 IU/kg (max 18,000 IU/ s.c. daily for one month) then 150 IU/kg (max 18,000 IU s.c. daily for five months (FRAGMIN arm) or FRAGMIN 200 IU/kg (max 18,000 IU s.c. daily for five to seven days and oral anticoagulant for six months (OAC arm). In the OAC arm, oral anticoagulation was adjusted to maintain an INR of 2 to 3. Patients were evaluated for recurrence of symptomatic venous thromboembolism (VTE) every two weeks for six months. The median age of patients was 64 years (range: 22 to 89 years); 51.5% of patients were females; 95.3% of patients were Caucasians. Types of tumors were:

gastrointestinal tract (23.7%), genito-urinary (21.5%), breast (16%), lung (13.3%), hematological tumors (10.4%) and other tumors (15.1%). Venous thrombotic events were adjudicated by a blinded central committee. A total of 27 (8.0%) and 53 (15.7%) patients in the FRAGMIN and OAC arms, respectively, experienced at least one episode of an objectively confirmed, symptomatic DVT and/or PE during the 6-month study period. Most of the difference occurred during the first month of treatment (see Table 3). The benefit was maintained over the 6-month study period.

Table 3
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 randomized patients, the primary comparison of the cumulative probability of the first VTE recurrence over the 6-month study period was statistically significant (p = 0.0017) in favor of the FRAGMIN arm, with most of the treatment difference evident in the first month.

Paediatric population

There is limited safety and efficacy information on the use of dalteparin in paediatric patients. If dalteparin is used in these patients, anti-Factor Xa levels should be monitored.

The largest prospective study investigated the efficacy, safety and relation of dose to plasma anti-Factor Xa activity of dalteparin in prophylaxis and therapy of arterial and venous thrombosis in 48 paediatric patients (Nohe et al, 1999).

Nohe et al (1999) Study Demographics and Trial Design

Trial design	Patients	Diagnosis	Indication, Fragmin Dose, Target anti-Factor Xa, Duration		
Single-center, open label trial; (n = 48)	Age: 31 week preterm to 18 years Gender: 32 males, 16 females	Arterial or venous thrombosis; PVOD; PPH	Prophylaxis: (n = 10) 95 ± 52 anti-Factor Xa IU/kg sc qd; 0.2 to 0.4 IU/ml 3-6 months	Primary Therapy: (n = 25) 129 ± 43 anti-Factor Xa IU/kg sc qd; 0.4 to 1.0 IU/ml 3-6 months	Secondary Therapy: (n = 13) 129 ± 43 anti-Factor Xa IU/kg sc qd; 0.4 to 1.0 IU/ml 3-6 months

In this study, no thromboembolic events occurred in the 10 patients receiving dalteparin for thromboprophylaxis. In the 23 patients given dalteparin for primary antithrombotic therapy of arterial or venous thrombosis, complete recanalization was seen in 7/23 (30%), partial recanalization in 7/23 (30%) and no recanalization in 9/23 (40%). In the 8 patients administered dalteparin for secondary antithrombotic therapy following successful thrombolysis, recanalisation was maintained or improved. In the 5 patients receiving dalteparin for secondary therapy following failed thrombolysis, no recanalization was seen. Minor bleeding, reported in 2/48 children (4%), resolved after dose reduction. Patient platelet counts ranged from 37,000/microl to 574,000/microl. The authors attributed platelet counts below normal (150,000/µl) to immunosuppressive therapy. A reduction in platelet count ≥50% of the initial value, a sign of heparin-induced thrombocytopenia type 2 (HIT 2), was not observed in any patient. For both prophylaxis and therapy groups, the dalteparin doses (anti-Factor Xa IU/kg) required to achieve target anti-Factor Xa activities (IU/ml) were inversely related to age ($r^2 = 0.64$, P = 0.017; $r^2 = 0.13$, P = 0.013). The predictability of the anticoagulant effect with weight-adjusted doses appears to be reduced in children compared to adults, presumably due to altered plasma binding (see section 5.2 **Pharmacokinetic properties**).

5.2 Pharmacokinetic Properties

Pharmacokinetics and Metabolism

Absorption - Absolute bioavailability in healthy volunteers, measured as the anti-Factor Xa activity, was 87 ± 6%. Increasing the dose from 2500 to 10,000 IU resulted in an overall increase in anti-Factor Xa AUC that was proportionally greater by about one-third.

Distribution - The volume of distribution for dalteparin anti-Factor Xa activity was 40 to 60 ml/kg.

Metabolism - Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer apparent terminal half-lives (3 to 5 hours) are observed following s.c. dosing, possibly due to delayed absorption.

Bioavailability after s.c. injection is about 90% and the pharmacokinetics are fundamentally not dose-dependent.

Excretion - Dalteparin is primarily excreted by the kidneys, however, the biological activity of the renally eliminated fragments is not well characterized. Less than 5% of anti-Factor Xa activity is detectable in the urine. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single intravenous bolus doses of 30 and 120 anti-Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 ml/hr/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 and 2.5 ± 0.3 hours.

Special Populations

Hemodialysis - In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Factor Xa activity following a single intravenous dose of 5000 IU dalteparin was 5.7 ± 2.0 hours, i.e. considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

Paediatric Population - Infants less than approximately 2 to 3 months of age or <5 kg have increased LMWH requirements per kg likely due to their larger volume of distribution. Alternative explanations for the increased requirement of LMWH per body weight in young children include altered heparin pharmacokinetics and/or a decreased expression of anticoagulant activity of heparin in children due to decreased plasma concentrations of antithrombin.

5.3 Preclinical Safety Data

The acute toxicity of dalteparin sodium is significantly lower compared to that of heparin.

In toxicological studies local haemorrhage at the injection site is the only significant observation reported constantly after subcutaneous administration of high doses. The incidence and severity of this phenomenon were dose-dependent. No cumulative effect occurred in the haemorrhages at the injection site.

The haemorrhagic reaction led to dose-dependent changes in the anticoagulant effect, as measured by the APTT and the anti-Factor Xa activity.

The osteoporosis effect of dalteparin sodium does not exceed that of heparin.

Carcinogenesis, Mutagenesis, Impairment of Fertility - Irrespective of method of administration, dose or treatment period, no organotoxicity was noted. No mutagenic effects were noted. No embryotoxic, fetotoxic or teratogenic effects, and no effects on fertility, copulation or peri- and post-natal development were noted when tested in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Single dose syringe of 2500 IU and graduated syringe of 10000 IU: Sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

Single dose syringe of 5000 IU and 7500 IU: Sodium hydroxide, hydrochloric acid and water for injection.

10 ml multidose vial: Benzyl alcohol as preservative, sodium hydroxide, hydrochloric acid and water for injection.

6.2 Incompatibilities

Compatibility between FRAGMIN and products other than those mentioned under Section 4.2 has not been investigated.

6.3 Shelf Life

Single dose - 36 months
MDV 10 ml - 24 months

6.4 Special Precautions for Storage

FRAGMIN can be stored below 30°C. It should not be frozen. FRAGMIN must not be used after the expiry date printed on the label. FRAGMIN solution for injection with preservative in vials should not be used later than 14 days after first opening of the vial.

6.5 Nature and Contents of Container

How supplied
Solution for injection 2500 IU (anti-Factor Xa)/0.2 ml, single dose syringes 10 x 0.2 ml
Solution for injection 5000 IU (anti-Factor Xa)/0.2 ml, single dose syringes 10 x 0.2 ml
Solution for injection 7500 IU (anti-Factor Xa)/0.3 ml, single dose syringes 5 x 0.3 ml
Solution for injection 10000 IU (anti-Factor Xa)/1 ml, single dose graduated syringes 5 x 1 ml
1 multidose vial of 10 ml containing 10000 IU (anti-Factor Xa) containing 14 mg of benzyl alcohol as preservative.

Pre-filled syringes (with or without Needle-Trap)
Solution for injection is supplied in a single dose pre-filled syringe (Type I glass) with a needle shield (rubber), a plunger stopper (chlorobutyl rubber), a plunger rod (polypropylene or polystyrene) and with or without a Needle-Trap as a safety feature. The needle shield may contain latex (see section 4.4).

6.6 Special Precautions for Disposal of a Used Medicinal Product or Waste Materials Derived from Such Medicinal Product and Other Handling of the Product

Discard any unused solution 14 days after first penetration of the multidose vial.

Using the vials, the ampoules and the pre-filled syringes:
No special requirements.
Use as per the standard protocol.