# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Fragmin®15,000 IU/0.6ml solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fragmin 15,000 IU: single dose syringe containing dalteparin sodium 15,000 IU (anti-Factor Xa) in 0.6 ml solution for injection equivalent to 25,000 IU/ml.

Fragmin does not contain preservatives.

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

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of venous thromboembolism (VTE) presenting clinically as deep vein thrombosis (DVT), pulmonary embolism (PE) or both.

Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence.

Paediatric population
Treatment of symptomatic venous thromboembolism (VTE) in paediatric patients 1 month of age and older.

### 4.2 Posology and method of administration

**Treatment of venous thromboembolism (VTE) presenting clinically as deep vein thrombosis (DVT), pulmonary embolism (PE) or both:**

**Adults**
A single dose of Fragmin is administered subcutaneously, once daily according to the following weight ranges. Monitoring of the anticoagulant effect is not usually necessary.

| Weight (kg) | Dose |
|---|---|
| 46-56 | 10,000 IU |
| 57-68 | 12,500 IU |
| 69-82 | 15,000 IU |
| 83 and over | 18,000 IU |

Abbreviations: IU = International Unit

The single daily dose should not exceed 18 000 IU.

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

**Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence.**

**Month 1**
Administer Fragmin 200 IU/kg total body weight subcutaneously (SC) once daily for the first 30 days of treatment. The total daily dose should not exceed 18,000 IU daily.

| Body Weight (kg) | Dose (IU) |
|---|---|
| <46 | 7 500 |
| 46-56 | 10 000 |
| 57-68 | 12 500 |
| 69-82 | 15 000 |
| 83 and over | 18 000* |

*** Maximum dose of 18, 000 IU was used in patient weighing up to 132 kg in the CLOT study.**

In the case of chemotherapy-induced thrombocytopenia, Fragmin dose should be adopted as follows:
- In patients receiving Fragmin who experience platelet counts between 50,000 and 100,000/$mm^3$, the daily dose of Fragmin should be reduced 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/$mm^3$.

**Months 2-6**
Fragmin should be administered at a dose of approximately 150 IU/kg, subcutaneously, once daily using fixed dose syringes and the table shown below.

| Body Weight (kg) | Dose (IU) |
|---|---|
| ≤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 will 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.

In the case of chemotherapy-induced thrombocytopenia, Fragmin dose should be adopted as follows:

- With platelet counts <50,000/mm$^3$, Fragmin dosing should be interrupted until the platelet count recovers above 50,000/mm$^3$
- For platelet counts between 50,000 and 100,000/mm$^3$, Fragmin should be reduced as illustrated in the table below depending on the patient's weight. Once the platelet count has recovered to ≥100,000/mm$^3$, Fragmin should be re-instituted at full dose.

| Body Weight (kg) | Scheduled Fragmin Dose (IU) | Reduced Fragmin Dose (IU) |
|---|---|---|
| ≤56 | 7 500 | 5 000 |
| 57 to 68 | 10 000 | 7 500 |
| 69 to 82 | 12 500 | 10 000 |
| 83 to 98 | 15 000 | 12 500 |
| ≥99 | 18 000 | 15 000 |

**Renal failure*:***
In the case of significant renal failure, defined as a creatinine clearance <30 ml/min, the dose of Fragmin should be adjusted based on anti-Factor Xa activity. If the anti-Factor Xa level is below or above the desired range, the dose of Fragmin should be increased or reduced respectively, and the anti-Factor Xa measurement should be repeated after 3-4 new doses. This dose adjustment should be repeated until the desired anti-Factor Xa level is achieved.

As an indication, on the basis of the data available in CLOT, the observed mean levels (min, max) between 4 and 6 hours after administration in patients without severe renal insufficiency were 1.11 IU anti-Factor Xa/ml (0.6; 1.88) and 1.03 IU anti-Factor Xa/ml (0.54; 1.70), respectively, on week 1 and 4 of dalteparin 200 IU/kg OD. Anti-Factor Xa activity determinations were conducted by the chromogenic method.

For patients with an increased risk of bleeding, it is recommended that Fragmin be administered according to the twice daily regimen detailed in the

Summary of Product Characteristics for Fragmin 10,000 IU/1ml ampoules or Fragmin Multidose Vial.

Paediatric population
Treatment of symptomatic venous thromboembolism (VTE) in paediatric patients 1 month of age and older.

A concentration of 2,500 IU/ml is recommended to ensure accuracy of dosing for the youngest age cohort. When dilution is required, it should be performed by a healthcare professional (see section 6.6). For children under 3 years of age, a presentation without benzyl alcohol should be used.

*Treatment of symptomatic venous thromboembolism in paediatric patients*
The recommended starting dose according to paediatric age is provided in the table below.

| **Starting doses for paediatric patients with symptomatic VTE** | |
|---|---|
| Age group | Starting dose |
| 1 month to less than 2 years | 150 IU/kg twice daily |
| 2 years to less than 8 years | 125 IU/kg twice daily |
| 8 years to less than 18 years | 100 IU/kg twice daily |

| **Paediatric dilution table** | | | |
|---|---|---|---|
| **Age** | **Recommended Concentration for Administration** | **Concentration as supplied*** | |
| | | **10,000 IU/ml**** | **25,000 IU/ml**** |
| 1 month - 2 years | 2,500 IU/ml | V (active) + 3V (diluent) | V (active) + 9V (diluent) |
| 2 years - 8 years | 10,000 IU/ml | No dilution required | V (active) + 1.5V (diluent) |
| 8 years - 17 years | 10,000 IU/ml | No dilution required | V (active) + 1.5V (diluent)*** |
| The final volume for injection should be between 0.15 ml and 1.0 ml; if it is below/above this range, a less/more concentrated (respectively) solution for administration should be prepared.<br>* Withdraw a convenient volume (V) of at least 1.0 ml of the solution as supplied and then add diluent (diluent volume is expressed as a multiple of V); administer the correct volume of the diluted solution. For children >20 kg, the 12,500 IU/ml concentration may also be administered directly, without dilution.<br>** The 10,000 IU/ml (10 ml vial) and 25,000 IU/ml (4 ml vial) multidose vials contain benzyl alcohol. For children under 3 years of age, a presentation without benzyl alcohol should be used.<br>*** For children >50 kg, the 25,000 IU/ml solution may also be administered directly, without dilution. | | | |

Fragmin is compatible with sodium chloride (9 mg/ml) or glucose (50 mg/ml) infusion solutions in glass bottles and plastic containers (see section 6.6).

**Monitoring Anti-Xa levels in children**
After initiation of Fragmin, anti-Xa level should initially be measured after the first, second or third dose. Samples for anti-Xa level should be drawn 4 hours after administration.

Doses should be adjusted in increments of 25 IU/kg to achieve target anti-Xa level between 0.5 IU/ml and 1 IU/ml and anti-Xa level measured after each

adjustment. The maintenance dose should be individualised based on the dose that achieves target anti-Xa level collected 4 hours after administration.

Monitoring of anti Xa levels should be continued until an adequate maintenance dose is established and continued periodically to maintain target anti-Xa level. In the youngest children, initial monitoring of anti-Xa level is recommended to start after the first dose and more frequent monitoring may be required afterwards to guide dose adjustments until the target anti-Xa levels are achieved (see sections 5.1 and 5.2).

In the case of low and changing physiologic renal function such as in neonates, close monitoring of anti-Xa levels is warranted.

As with all antithrombotic agents, there is a risk of systemic bleeding with Fragmin administration. Care should be taken with Fragmin use in high dose treatment of newly operated patients. 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 hemoglobin, and anti-Xa determinations.

The safety and efficacy of dalteparin sodium for prophylaxis of VTE in children has not been established. Currently available data on prophylaxis of VTE are described in section 5.1 but no recommendation on a posology can be made.

Elderly

Fragmin has been used safely in elderly patients without the need for dosage adjustment.

Method of administration

By subcutaneous injection, preferably into the abdominal subcutaneous tissue anterolaterally or posterolaterally, or into the lateral part of the thigh. Patients should be supine and the total length of the needle should be introduced vertically, not at an angle, into the thick part of a skin fold, produced by squeezing the skin between thumb and forefinger; the skin fold should be held throughout the injection.

*Paediatric population*
Fragmin is administered by subcutaneous administration, preferably into the abdominal subcutaneous tissue anterolaterally or posterolaterally, or into the lateral part of the thigh at an angle between 45° and 90°.
Comprehensive instructions for the administration of Fragmin are given in section 3 of the package leaflet.

## 4.3 Contraindications

Known hypersensitivity to Fragmin or other low molecular weight heparins and/or heparins e.g. history of confirmed or suspected immunologically mediated heparin induced thrombocytopenia (type II); acute gastroduodenal ulcer; cerebral haemorrhage; known haemorrhagic diathesis or other active haemorrhage; serious coagulation disorders; acute or sub-acute septic endocarditis; haemorrhagic pericardial effusion and haemorrhagic pleural effusion; injuries to and operations on the central nervous system, eyes and ears.

In patients receiving Fragmin for treatment rather than prophylaxis, local and/or regional anaesthesia in elective surgical procedures is contra-indicated with high doses of dalteparin (such as those needed to treat acute deep-vein thrombosis, pulmonary embolism, and unstable coronary artery disease).

In cancer patients with body weight < 40kg at time of venous thromboembolic event, Fragmin should not be used for extended treatment of symptomatic VTE and prevention of its recurrences due to lack of data.

Dalteparin should not be used in patients who have suffered a recent (within 3 months) stroke unless due to systemic emboli.

## 4.4 Special warnings and precautions for use

Do not administer by the intramuscular route. Due to the risk of haematoma, intramuscular injection of other medical preparations should be avoided when the twenty-four hour dose of dalteparin exceeds 5,000 IU.

Caution should be exercised in patients in whom there is an increased risk of bleeding complications, e.g. following surgery or trauma, haemorrhagic stroke, severe liver or renal failure, thrombocytopenia or defective platelet function, uncontrolled hypertension, hypertensive or diabetic retinopathy, patients receiving concurrent anticoagulant/antiplatelet agents (see section 4.5). Caution shall also be observed at high-dose treatment with dalteparin (such as those needed to treat acute deep-vein thrombosis, pulmonary embolism, and unstable coronary artery disease).

The concomitant use with drugs affecting hemostasis, 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).

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.

Thrombocytopenia, should it occur, usually appears within three weeks following the beginning of therapy. Therefore, it is recommended that the platelet counts are measured before starting treatment with Fragmin and monitored closely in first three weeks and regularly thereafter during the treatment. Special caution is necessary in rapidly developing thrombocytopenia and severe thrombocytopenia (<100,000/µl) associated with positive or unknown results of in-vitro tests for anti-platelet antibody in the presence of Fragmin or other low molecular weight (mass) heparins and/or heparin.

Fragmin induces only a moderate prolongation of the APTT and thrombin time. Accordingly, dosage increments based upon prolongation of the APTT may cause overdosage and bleeding. Therefore, prolongation of the APTT should only be used as a test of overdosage.

**Monitoring Anti-Xa Levels**
Monitoring of Anti-Xa Levels in patients using Fragmin is not usually required but should be considered for specific patient populations such as paediatrics those with renal failure, those who are very thin or morbidly obese, pregnant or at increased risk for bleeding or rethrombosis.

Where monitoring is necessary, laboratory assays using a chromogenic substrate are considered the method of choice for measuring anti-Xa levels. Activated partial thromboplastin time (APTT) or thrombin time should not be used because these tests are relatively insensitive to the activity of dalteparin. Increasing the dose of dalteparin in an attempt to prolong APTT may result in bleeding (see section 4.9).

Patients under chronic haemodialysis with dalteparin need as a rule fewer dosage adjustments and as a result fewer controls of anti-Xa levels. Patients undergoing acute haemodialysis may be more unstable and should have a more comprehensive monitoring of anti-Xa levels (see section 5.2).

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

If a transmural myocardial infarction occurs in patients where thrombolytic treatment might be appropriate, this does not necessitate discontinuation of treatment with Fragmin but might increase the risk of bleeding.

As individual low molecular weight (mass) heparins have differing characteristics, switching to an alternative low molecular weight heparin should be avoided. The directions for use relating to each specific product must be observed as different dosages may be required.

**Interchangeability with other anticoagulants**
Dalteparin cannot be used interchangeably (unit for unit) with unfractionated heparin, other low molecular weight heparins, or synthetic polysaccharides. Each of these medicines differ in their starting raw materials, manufacturing

process, physico-chemical, biological, and clinical properties, leading to differences in biochemical identity, dosing and possibly clinical efficacy and safety. Each of these medicines is unique and has its own instructions for use.

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, a 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.

When neuraxial anaesthesia (epidural/spinal anaesthesia) or spinal puncture is employed, patients are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis, such as nonsteroidal 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 when anticoagulation is given in connection with epidural/spinal anaesthesia.

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.

Should a physician, as a clinical judgement, decide to administer anticoagulation in the context of epidural or spinal anaesthesia, 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. Nurses should be trained to detect such signs and symptoms. Patients should be instructed to inform immediately a nurse or a clinician if they experience any of these.

If signs or symptoms of epidural or spinal haematoma are suspected, urgent diagnosis and treatment may include spinal cord decompression.

There have been no adequate studies to assess the safe and effective use of Fragmin in preventing valve thrombosis in patients with prosthetic heart valves. Prophylactic doses of Fragmin are not sufficient to prevent valve thrombosis in patients with prosthetic heart valves. The use of Fragmin cannot be recommended for this purpose.

At long-term treatment of unstable coronary artery disease, such as e.g., before revascularisation, dose reduction should be considered at reduced kidney function (S-creatinine > 150 μmol/l)**.**

Paediatric population
Anti-Xa levels should be monitored during initiation of therapy and following any dose adjustment (see section 4.2).

There are no data in children with cerebral vein and sinus thrombosis who have a CNS infection. The risk of bleeding should be carefully evaluated before and during therapy with dalteparin.

Use in 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.

**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).

Excipients
*Sodium*
Fragmin 15,000 IU (anti-Xa)/0.6 ml contains less than 1 mmol (23 mg) of sodium per pre-filled syringe, i.e. that is to say essentially "sodium-free". Patients on low sodium diets and parents whose children receive treatment with Fragmin can be informed that this medicinal product formulation is essentially ‘sodium-free’.

This medicinal product may be further diluted with sodium-containing solutions (see section 4.2 and section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

## 4.5 Interaction with other medicinal products and other forms of interaction

**Drugs Increasing Effects of Dalteparin**
The possibility of the following interactions with Fragmin should be considered:

i) An enhancement of the anticoagulant effect by other anticoagulant/ antiplatelet agents e.g. aspirin/dipyridamole, GP IIb/IIIa receptor antagonists, Vitamin K antagonists, NSAIDs e.g. indometacin, cytostatics, dextran, thrombolytics, sulfinpyrazone, probenecid, and etacrynic acid (see section 4.2 and section 4.4).
ii) A reduction of the anticoagulant effect may occur with concomitant administration of antihistamines, cardiac glycosides, tetracycline and ascorbic acid.

Because NSAIDs and ASA 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 ASA in patients with renal failure.

However, if there are no specific contraindications, patients with unstable coronary artery disease (unstable angina and non-Q-wave infarction) shall be treated with low doses of acetylsalicylic acid.

**Drugs Antagonizing Effects of Dalteparin**
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.

**Other Interactions**
As heparin has been shown to interact with intravenous nitroglycerine, high dose penicillin, quinine and tobacco smoking, interaction cannot be ruled out for dalteparin.

**Paediatric population**
Interaction studies have only been studied in adults.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Dalteparin does not pass the placenta. A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity. Fragmin can be used during pregnancy if clinically needed.

If dalteparin is used during pregnancy, the possibility of foetal harm appears remote. However, because the possibility of harm cannot be completely ruled out, dalteparin should be used during pregnancy only if clearly needed.

There are more than 2,000 published cases (studies, case series and case reports) on administration of dalteparin in pregnancy. As compared with unfractionated heparin, a lower bleeding tendency and reduced risk of osteoporotic fracture was reported. The largest prospective study “Efficacy of Thromboprophylaxis as an Intervention during Gravidity” (EThIG), involved 810 pregnant women and investigated a pregnancy-specific scheme for risk stratification (low, high, very high risk of venous thromboembolism) with daily doses of dalteparin between 50 – 150 IU/kg body weight (in single cases up to max. 200 IU/kg body weight). However, only limited randomised controlled studies are available on the use of low molecular weight heparins in pregnancy.

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

Epidural anaesthesia during childbirth is absolutely contraindicated in women who are being treated with high-dose anticoagulants (see section 4.3). Caution is recommended when treating patients with an increased risk of haemorrhage, such as perinatal women (see section 4.4). In pregnant women during the last trimester, dalteparin anti-Xa half-lives of 4 to 5 hours were measured.

Fragmin 100,000 IU/4ml multidose vial contains benzyl alcohol as a preservative. As benzyl alcohol may cross the placenta, Fragmin without preservative should therefore be used during pregnancy.

Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anti-coagulant doses of low molecular weight heparin. In the absence of clear dosing, efficacy and safety information in this circumstance, Fragmin is not recommended for use in pregnant women with prosthetic heart valves.

Breast-feeding
Limited data are available for excretion of dalteparin in human milk. One study in 15 women ( between day 3 and 5 of lactation and 2 to 3 hours after receiving prophylactic doses of dalteparin) detected small amounts of anti- factor Xa levels of 2 to 8% of the plasma levels in breast milk, equivalent to a milk/plasma ratio of <0.025-0.224. An anticoagulant effect on the infant appears unlikely.

A risk to the suckling child cannot be excluded. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Fragmin should be made taking into account the benefit of breast-feeding to the child and the benefit of Fragmin therapy to the woman.

Fertility
Based on current clinical data there is no evidence that dalteparin sodium affects fertility. No effects on fertility, copulation or peri- and postnatal development were noted when dalteparin sodium was tested in animals.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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).

| *System Organ Class* | *Frequency* | *Adverse reactions* |
|---|---|---|
| Blood and lymphatic system disorders | Common | Mild thrombocytopenia (type I), which usually is reversible during the treatment |
| | Not Known* | Immunologically-mediated heparin-induced |

| | | |
|---|---|---|
| | | thrombocytopenia (type II, with or without associated thrombotic complications) |
| Immune system disorders | Uncommon | Hypersensitivity |
| | Not Known* | Anaphylactic reactions |
| Metabolism and nutrition disorders | Common | Hyperkalaemia |
| Nervous system disorders | Not Known* | Intracranial bleeds have been reported and some have been fatal |
| Cardiac disorders | Not Known* | Prosthetic cardiac valve thrombosis |
| Vascular disorders | Common | Haemorrhage |
| Gastrointestinal disorders | Not Known* | Retroperitoneal bleeds have been reported and some have been fatal |
| Hepatic and biliary disorders | Common | Transient elevation of transaminases |
| Skin and subcutaneous tissue disorders | Uncommon | Urticaria, pruritus |
| | Rare | Skin necrosis, transient alopecia |
| | Not Known* | Rash |
| Musculoskeletal and connective tissue disorders | Uncommon | Osteoporosis (in connection with long-term treatment) |
| General disorders and administration site conditions | Common | Subcutaneous haematoma at the injection site<br>Pain at the injection site |
| Injury, Poisoning and Procedural Complications | Not Known* | Spinal or epidural hematoma |

*(cannot be established from available data)

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).

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

The anticoagulant effect (i.e. prolongation of the APTT) induced by Fragmin is inhibited by protamine. Since protamine itself has an inhibiting effect on primary haemostasis it should be used only in an emergency. The prolongation of the clotting time induced by Fragmin may be fully neutralised by protamine, but the anti-Factor Xa activity is only neutralised to about 25-50%. 1mg of protamine inhibits the effect of 100 IU (anti-Factor Xa) of Fragmin.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC Code B01AB 04: Antithrombotics

Dalteparin sodium is a low molecular weight heparin fraction (weight average molecular weight of 6000 Daltons (range between 5,600 and 6,400 Daltons)) produced from porcine-derived heparin sodium.

Mechanism of action

Dalteparin sodium is an antithrombotic agent, which acts mainly through its ability to potentiate the inhibition of Factor Xa and thrombin by antithrombin. It has a relatively higher ability to potentiate Factor Xa inhibition than to prolong plasma clotting time (APTT).

Pharmacodynamic effects

Compared with standard, unfractionated heparin, dalteparin sodium has a reduced adverse effect on platelet function and platelet adhesion, and thus has only a minimal effect on primary haemostasis. Still some of the antithrombotic properties of dalteparin sodium are thought to be mediated through the effects on vessel walls or the fibrinolytic system.

Clinical efficacy and safety

The randomized, open-label, controlled, multicenter CLOT study (Randomized Comparison of Low-Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer patients with Venous Thomboembolism) compared dalteparin to standard oral anticoagulant (OAC) therapy in the long term treatment of venous thromboembolism (VTE) in 676 patients with active malignancy who had experienced an acute symptomatic VTE (deep venous thrombosis (DVT) and/or a pulmonary embolism (PE)).

Patients were randomized to one of two groups:

- dalteparin arm prescribed at 200 IU/kg/day administered by subcutaneous (SC) injections (maximum 18,000 IU/day) during 1 month, then approximately 150 IU/kg/day from 2$^{nd}$ – 6th month, or

- VKA arm prescribed during 6 months (target INR 2-3), preceded by SC dalteparin 200 IU/kg/day OD (maximum 18,000 IU/day) during 5 to 7 days.
The most frequent diagnoses were: tumors of the gastrointestinal tract and pancreas (23.7%), genitourinary tumors (prostate, testicle, cervix, uterus, ovary and bladder) (21.5%), breast (16.0%), lung (13.3%). 10.4% of patients had haematological malignancies ; 75.1% of patients had metastatic disease.
The index VTE event was DVT alone in nearly 70% and PE with or without DVT in 30% of patients.
The primary endpoint was the time to first recurrence of symptomatic VTE (DVT and/or PE) during 6 months.
A total of 27 patients of 338 (8.0%) in the dalteparin arm and 53 patients of 338 (15.7%) in the VKA arm experienced at least one of the events of the composite primary endpoint. A significant 52% risk reduction in VTE recurrence at 6 months was seen with dalteparin (RR= 0.48, 95% CI [0.30-0.77], p=0.0016).
In the dalteparin arm, 19 patients (5.6%) experienced at least one episode of major bleeding compared to 12 patients (3.6%) in the VKA arm. The cumulative probability of experiencing a major bleeding at 6 months was respectively 6.5% and 4.9%, respectively. Any bleeding occurred with a higher frequency in the VKA arm (18.5% VKA vs 13.6% dalteparin). The comparison of the cumulative probability of first bleeding episode for the 2 treatments was of statistical significance in favour of dalteparin treatment (p=0.0487).
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 VKA arms, respectively).

There was no significant difference in the assessment of Quality of Life between the two groups of treatment.

Paediatric population

*Treatment of symptomatic venous thromboembolism (VTE) in paediatric patients*

An open-label, multi-centre, Phase 2 clinical trial studied 38 paediatric patients with objectively diagnosed acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE). (24 males; 14 females) representing 5 age cohort groups, with cancer (N=26) and without cancer (N= 12). A total of 26 patients completed the study and 12 prematurely discontinued (4 due to adverse events, 3 patients withdrew consent and 5 for other reasons). The patients were treated with dalteparin twice daily for up to 3 months, with starting doses by age and weight and using a dose adjustment increment of 25 IU/kg.

The efficacy of the treatment in terms of regression, progression, resolution or no change in the qualifying VTE was assessed by imaging modalities at screening and at the end of the study (EOS).

At study completion (N=34), 21 (61.8%) patients had achieved resolution of the qualifying VTE; 7 (20.6%) patients showed regression, 2 (5.9%) patients

showed no change, no patients showed progression and 4 (11.8%) patients did not contribute data for this analysis. In addition, 1 (2.9%) patient experienced a new VTE during the study.

The median doses of dalteparin (IU/kg) required to achieve a therapeutic anti-Xa level (0.5 to 1.0 IU/ml) during the 7-day dose adjustment period are presented in Table 1. Therapeutic anti-Xa levels (0.5 to 1.0 IU/ml) were achieved within (mean) 2.6 days. Bleeding events in patients who received at least one dose of study drug (N=38) included 1 (2.6%) major bleeding event; 0 (0%) clinically relevant non-major bleeding events; 16 (42.1%) minor bleeding events; and 14 (36.8%) patients had no bleeding events.

Table 1 - Median maintenance doses of dalteparin (IU/kg) after dose adjustment (using 25 IU/kg increments) associated with therapeutic anti-Xa level (0.5 to 1.0 IU/ml) by age cohort (N=34)

| Age cohort | N | Median dose (IU/kg) |
|---|---|---|
| 0 to less than 8 weeks | 0 | N/A |
| Greater than or equal to 8 weeks to less than 2 years | 2 | 208 |
| Greater than or equal to 2 years to less than 8 years | 8 | 128 |
| Greater than or equal to 8 years to less than 12 years | 7 | 125 |
| Greater than or equal to 12 years to less than 19 years | 17 | 117 |

A prospective, multi-centre, randomised, controlled clinical trial evaluated the duration of therapy for thrombosis in 18 children (0 to 21 years) receiving dalteparin anticoagulant treatment twice daily and determined the dalteparin dose per kilogram required to achieve an anti-Xa level of 0.5-1.0 IU/ml at 4-6 hours post-dose, by age group (pre-specified as infants <12 months, children 1 - <13 years, and adolescents 13 - <21 years).

The results from this study showed that median (range) therapeutic doses by age group were as follows: infants (n=3), 180 IU/kg (146-181 IU/kg); children (n=7), 125 IU/kg (101-175 IU/kg); and adolescents (n=8), 100 IU/kg (91-163 IU/kg).

A retrospective analysis reviewed the clinical and laboratory outcomes of prophylactic and therapeutic use of dalteparin in children (0 - 18 years old) in a single institution (Mayo Clinic) for VTE treatment from 1 December 2000 through 31 December 2011.

Treatment data for a total of 166 patients were reviewed, including 116 patients who received prophylactic doses of dalteparin and 50 patients who received therapeutic doses. The 50 patients receiving therapeutic doses, either once or twice per day, included 13 patients under 1 year of age and 21 patients with malignancies. The results showed that patients under 1 year of age required significantly higher weight-based dosage to achieve therapeutic anti-Xa levels compared to children (1-10 years) or adolescents (>10-18 years) (mean dose units/kg/day; 396.6 versus 236.7 and 178.8 respectively, $p < 0.0001$).

Of the 50 children treated in this retrospective study, 17 were infants under 2 years of age (mean age 6 months; 10/17 male). Most infants (12/17) were dosed twice a day with a median dalteparin starting dose of 151 IU/kg; (range 85 – 174 IU/kg); 5 infants were dosed only once a day, with similar doses. The 17 infants were treated for 1 to 3 months (median 2 months) and resolution of the VTE occurred in 82%; none experienced bleeding complications or ADR related to dalteparin.

*Prophylaxis of venous thromboembolism in paediatric patients*

A prospective study (Nohe et al, 1999) investigated the efficacy, safety and relation of dose to plasma anti-Xa activity of dalteparin in prophylaxis and therapy of arterial and venous thrombosis in 48 paediatric patients (32 males, 16 females; 31 weeks preterm to 18 years of age). Eight children with risk factors for thrombosis (obesity, protein C deficiency, carcinoma) received dalteparin for immobilization prophylaxis and 2 for "high risk" prophylaxis after cardiac surgery (group I). Thirty-six children received dalteparin therapeutically after arterial or venous thromboembolic events (groups II-IV). In the therapy group, 8/36 children (22%) were treated with dalteparin for reocclusion prophylaxis following successful thrombolytic therapy (group II), 5/36 (14%) following inferior failed thrombolytic therapy with rtPA or urokinase (group III) and 23/36 (64%) for primary antithrombotic therapy because of contraindications for thrombolysis (group IV).

In this study, 10 patients who received dalteparin for thromboprophylaxis required a maintenance dose of 95 ± 52 IU/kg subcutaneous (SC) once daily in order to achieve anti-Xa level of 0.2 to 0.4 IU/ml over a duration of 3 to 6 months. No thromboembolic events occurred in the 10 patients receiving dalteparin for thromboprophylaxis.

## 5.2 Pharmacokinetic properties

Elimination
The half life following i.v. and s.c. administration is 2 hours and 3.5-4 hours respectively, twice that of unfractionated heparin.

Bioavailability
The bioavailability following s.c. injection is approximately 87 per cent and the pharmacokinetics are not dose dependent. The half life is prolonged in uraemic patients as dalteparin sodium is eliminated primarily thought the kidneys.

**Special Populations**
**Haemodialysis**
In patients with chronic renal insufficiency requiring haemodialysis, the mean terminal hal-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**

The pharmacokinetics of twice-daily subcutaneous (SC) dalteparin, measured as anti-Factor Xa activity, was characterised in 89 paediatric subjects with or without cancer from two clinical studies and 1 observational study. Dalteparin pharmacokinetics (PK) were described by a 1-compartment model with linear absorption and elimination and PK parameters are shown in Table 2. After correcting for the body weight, clearance (CL/F) decreased with increasing age, while volume of distribution at steady-state ($V_d$/F) remained similar. The mean elimination half-life increased with age.

Table 2 - Pharmacokinetic parameters of dalteparin in paediatric population

| Parameter | Birth to < 8 weeks | ≥ 8 weeks to < 2 years | ≥ 2 years to < 8 years | ≥ 8 years to < 12 years | ≥ 12 years to < 19 years |
|---|---|---|---|---|---|
| Number of patients (N) | 6 | 13 | 14 | 11 | 45 |
| Median age (range) (years) | 0.06 (0.04 – 0.14) | 0.5 (0.2 – 1.91) | 4.47 (2.01 – 7.6) | 9.62 (8.01 – 10.5) | 15.9 (12.0 – 19.5) |
| Derived mean (SD) CL/F (ml/h/kg) | 55.8 (3.91) | 40.4 (8.49) | 26.7 (4.75) | 22.4 (3.40) | 18.8 (3.01) |
| Derived mean (SD) $V_d$/F (ml/kg) | 181 (15.3) | 175 (55.3) | 160 (25.6) | 165 (27.3) | 171 (38.9) |
| Derived mean (SD) $t_{½\beta}$ (h) | 2.25 (0.173) | 3.02 (0.688) | 4.27 (1.05) | 5.11 (0.509) | 6.28 (0.937) |

CL=clearance; F=Absolute bioavailability; SD=standard deviation; $t_{½\beta}$=elimination half-life; $V_d$=volume of distribution.

### 5.3 Preclinical safety data

The acute toxicity of dalteparin sodium is considerably lower than that of heparin. The only significant finding, which occurred consistently throughout the toxicity studies after subcutaneous administration of the higher dose levels, was local haemorrhage at the injection sites, dose-related in incidence and severity. There was no cumulative effect on injection site haemorrhages.

The haemorrhagic reaction was reflected in dose related changes in the anticoagulant effects as measured by APTT and anti-Factor Xa activities.

It was concluded that dalteparin sodium may have an osteopenic effect at very high concentrations, and that this effect is less than that of unfractionated heparin at equivalent doses.

The results revealed no organ toxicity irrespective of the route of administration, doses or duration of treatment. No mutagenic effect was found. No embryotoxic or teratogenic effects and no effect on fertility reproductive capacity or peri- and postnatal development was shown.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Water for Injections (Ph. Eur.)
Sodium hydroxide or hydrochloric acid for pH adjustment

## 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

3 years.

From a microbiological point of view, unless the method of opening and dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

## 6.4 Special precautions for storage

Store below 25ºC

## 6.5 Nature and contents of container

Fragmin 15 000 IU/0.6ml 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 (polystyrene) and a needle-trap as a safety feature. The needle shield may contain latex (see section 4.4).
Each pack contains 5 syringes.

## 6.6 Special precautions for disposal

The Needle-Trap consists of a plastic needle “catcher” which is firmly attached to the syringe label. Together, these two components comprise the Needle-Trap (safety) feature. The Needle-Trap is designed to specifically help prevent accidental needle sticks following the proper administration of injectable medications.

The Needle-Trap requires specific actions by the user to “activate” the Needle-Trap, which will render the needle harmless after the injection is administered:

- The user grasps the tip of the plastic needle catcher and bends it away from needle shield.
- The needle shield is removed from the syringe.
- The injection is administered normally.
- The needle is removed from the patient. The Needle-Trap is activated by placing the plastic catcher against a hard, stable surface and with one hand, pivoting the syringe barrel upward against the needle forcing the needle into the catcher where it locks in place (an audible ‘click” is heard when the needle is locked in the catcher). The needle is bent until the syringe exceeds a 45 degree angle with the flat surface to render it permanently unusable.
- The syringe is properly disposed of normally.

When dilution to a concentration of 2,500 IU/ml is required, Fragmin can be diluted with sodium chloride (9 mg/ml) or glucose (50 mg/ml) infusion solutions in glass bottles and plastic containers. See dilution table in section 4.2.

It is recommended that once diluted, the solution be used immediately (see section 6.3).

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

Comprehensive instructions for the administration of Fragmin are given in section 3 of the package leaflet.

## 7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
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CT13 9NJ
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## 8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/0981

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/03/2002

## 10 DATE OF REVISION OF THE TEXT

21/10/2025