Fragmin®

Dalteparin sodium

Solution for Injection

Reference market: Belgium

Common Export Pack

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fragmin 2,500 IU (anti-Xa)/0.2 ml, solution for injection
Fragmin 2,500 IU (anti-Xa)/ml, solution for injection
Fragmin 5,000 IU (anti-Xa)/0.2 ml, solution for injection
Fragmin 7,500 IU (anti-Xa)/0.3 ml, solution for injection
Fragmin 7,500 IU (anti-Xa)/0.75 ml, solution for injection
Fragmin 10,000 IU (anti-Xa)/ml, solution for injection
Fragmin 10,000 IU (anti-Xa)/0.4 ml, solution for injection
Fragmin 12,500 IU (anti-Xa)/0.5 ml, solution for injection
Fragmin 15,000 IU (anti-Xa)/0.6 ml, solution for injection
Fragmin 18,000 IU (anti-Xa)/0.72 ml, solution for injection
Fragmin 25,000 IU (anti-Xa)/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fragmin 2,500 IU (anti-Xa)/0.2 ml, solution for injection: each 0.2 ml syringe contains 2,500 IU (anti-Xa) dalteparin sodium, i.e. 12,500 IU/ml.
Fragmin 2,500 IU (anti-Xa)/ml, solution for injection: each 4 ml vial contains 10,000 IU (anti-Xa) dalteparin sodium, i.e. 2,500 IU/ml.
Fragmin 2,500 IU (anti-Xa)/ml, solution for injection: each 4 ml ampoule contains 10,000 IU (anti-Xa) dalteparin sodium, i.e. 2,500 IU/ml.
Fragmin 5,000 IU (anti-Xa)/0.2 ml, solution for injection: each 0.2 ml syringe contains 5,000 IU (anti-Xa) dalteparin sodium, i.e. 25,000 IU/ml.
Fragmin 7,500 IU (anti-Xa)/0.3 ml, solution for injection: each 0.3 ml syringe contains 7,500 IU (anti-Xa) dalteparin sodium, i.e. 25,000 IU/ml.
Fragmin 7,500 IU (anti-Xa)/0.75 ml, solution for injection: each 0.75 ml syringe contains 7,500 IU (anti-Xa) dalteparin sodium, i.e. 10,000 IU/ml.
Fragmin 10,000 IU (anti-Xa)/ml, solution for injection: each 1 ml syringe contains 10,000 IU (anti-Xa) dalteparin sodium.
Fragmin 10,000 IU (anti-Xa)/ ml, solution for injection: each 1 ml ampoule contains 10,000 IU (anti-Xa) dalteparin sodium.
Fragmin 10,000 IU (anti-Xa)/ml, solution for injection: each 10 ml vial contains 100,000 IU (anti-Xa) dalteparin sodium, i.e. 10,000 IU/ml.
Fragmin 10,000 IU (anti-Xa)/0.4 ml, solution for injection: each 0.4 ml syringe contains 10,000 IU (anti-Xa) dalteparin sodium, i.e. 25,000 IU/ml.
Fragmin 12,500 IU (anti-Xa)/0.5 ml, solution for injection: each 0.5 ml syringe contains 12,500 IU (anti-Xa) dalteparin sodium, i.e. 25,000 IU/ml.
Fragmin 15,000 IU (anti-Xa)/0.6 ml, solution for injection: each 0.6 ml syringe contains 15,000 IU (anti-Xa) dalteparin sodium, i.e. 25,000 IU/ml.
Fragmin 18,000 IU (anti-Xa)/0.72 ml, solution for injection: each 0.72 ml syringe contains 18,000 IU (anti-Xa) dalteparin sodium, i.e. 25,000 IU/ml.
Fragmin 25,000 IU (anti-Xa)/ml, solution for injection: each 4 ml vial contains 100,000 IU (anti-Xa) dalteparin sodium, i.e. 25,000 IU/ml.

(IU = international unit)

Excipient with known effect
Fragmin 10,000 IU (anti-Xa)/ml 10 ml vial and Fragmin 25,000 IU (anti-Xa)/ml 4 ml vial contain 14 mg/ml benzyl alcohol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Pre-filled syringes: subcutaneous use.
Ampoules: subcutaneous or intravenous use.
Vials containing 4 ml of Fragmin 2,500 IU (anti-Xa)/ml: intravenous use.
Vials containing 4 ml of Fragmin 25,000 IU (anti-Xa)/ml: subcutaneous or intravenous use.
Vials containing 10 ml of Fragmin 10,000 IU (anti-Xa)/ml: subcutaneous or intravenous use.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

1. Prevention of thromboembolic accidents:
   - More in particular in the pre-, peri- and postoperative period in abdominal, gynaecological, urologic (in both benign and malignant conditions) and orthopaedic surgery.
   - During haemodialysis.

2. Treatment of thromboembolic accidents: deep-vein thrombosis.

3. Fragmin is also indicated for treatment of the symptoms of venous thromboembolism (VTE) and for preventing the recurrence of VTE in patients with cancer.

4.2. Posology and method of administration

1. <u>Preventive treatment of thromboembolic accidents</u>

<u>Posology</u>

- *<u>In patients at moderate risk of thrombosis</u>*
  - The day of surgery: 1 to 2 hours before surgery, administer 2,500 IU anti-Xa.
  - The following days: once daily, administer 2,500 IU anti-Xa.

- *<u>In patients at additional risk of thrombosis (in particular patients with some forms of cancer and in some orthopaedic procedures, such as total hip replacement)</u>*
  1) Preoperative administration:
     - Either the evening before surgery: 5,000 IU anti-Xa.
     - Either the day of surgery: 1 to 2 hours before surgery, administer 2,500 IU anti-Xa and repeat the injection 12 hours later.

  2) Postoperative administration:
     The following days, administer 5,000 IU anti-Xa once daily or 2,500 IU anti-Xa twice daily (in the morning and the evening). Prophylactic treatment should be continued during the whole risk period (i.e. for at least 5 days and until the patient is fully mobilised). After total hip replacement, surgery treatment may be continued for up to 5 weeks after surgery even if the patient has been mobilised.

<u>Method of administration</u>
Subcutaneous administration.

Haemodialysis

Posology

- *In patients at increased risk of bleeding*
  - Initial dose: bolus injection of 5 to 10 anti-Xa IU/kg.
  - Maintenance dose: infusion of 4 to 5 anti-Xa IU/kg/ hour.

  The anti-Xa plasma levels should be within the range of 0.2 and 0.4 IU/ml.

- *In patients at low risk or at non-existent risk of bleeding*
  - Initial dose: bolus injection of 30 to 40 anti-Xa IU/kg.
  - Maintenance dose: infusion of 10 to 15 anti-Xa IU/kg/ hour.

- *In short-term haemodialysis (≤ 4 hours) the dosage described above can be replaced by*
  - Single dose: bolus injection of 80 anti-Xa IU/kg. This is usually a single injection of about 5,000 anti-Xa IU.
  - For flushing the tubing 2,500 anti-Xa IU is required.

In all these cases plasma anti-Xa activity should be within the range of 0.5 - 1 anti-Xa IU/ml.

Method of administration
Intravenous administration.

2. Curative treatment of thromboembolic accidents: deep-vein thrombosis

Posology
To treat acute deep-vein thrombosis Fragmin can be injected once or twice daily, either subcutaneously or via continuous intravenous infusion, preferably via an infusion pump.

- *Subcutaneous injection once daily*
  A dose of 200 IU/kg is administered subcutaneously once daily. The dose per single injection should not exceed 18,000 IU.

- *Subcutaneous injection twice daily*
  A dose of 100 IU/kg is administered subcutaneously twice daily with a 12-hour-interval; this posology scheme can be used in patients at increased risk of bleeding.
  In general it is not necessary to monitor treatment, but a functional anti-Xa-test can be used for this purpose. Maximal plasma levels are reached 3-4 hours after subcutaneous injection; samples for biological measurement of anti-Xa activity should be taken at this time. The recommended plasma levels are within the range of 0.5 - 1 anti-Xa/ml. If necessary, the initial posology should be adjusted.

- *Continuous intravenous infusion*
  The recommended initial dose is 100 IU/kg. This dose is administered over a period of 12 hours.

Method of administration
Subcutaneously or via continuous intravenous infusion, preferably via an infusion pump. For further details, see the posology section.

3. Treatment and prevention of venous thromboembolism in patients with cancer

Posology

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

- *Month 2-6*
  Fragmin should be administered at a dose of approximately 150 IU/kg, subcutaneously once daily, using fixed-dose syringes with the dose based on the patient's weight, in accordance with the table below:

Quantity of Fragmin to be administered subcutaneously based on the patient's weight	
Body weight (kg)	Fragmin dose (IU)
≤56	7,500
57 to 68	10,000
69 to 82	12,500
83 to 98	15,000
≥99	18,000

- *Dose reductions for chemotherapy-induced thrombocytopenia*
  Thrombocytopenia: in the case of chemotherapy-induced thrombocytopenia with platelet counts < 50,000/mm^3, administration of Fragmin should be interrupted until the platelet count recovers to above 50,000/mm^3.
  For platelet counts between 50,000 and 100,000/mm^3, the Fragmin dose should be reduced by 17% to 33% of the initial dose. The table below indicates the necessary dose reduction based on the patient's weight. Once the platelet count has recovered to ≥ 100,000/mm^3, Fragmin should be reinstituted at the full dose.

Dose reduction of Fragmin for thrombocytopenia 50,000-100,000/mm^3			
Body weight (kg)	Scheduled Fragmin dose (IU)	Reduced Fragmin dose (IU)	Mean dose reduction (%)
≤56	7,500	5,000	33
57 to 68	10,000	7,500	25
69 to 82	12,500	10,000	20
83 to 98	15,000	12,500	17
≥99	18,000	15,000	17

  Renal failure: in the case of significant renal failure, defined as a creatinine level more than three times the upper limit of normal, the dose of Fragmin should be adjusted to maintain an anti-Xa therapeutic level of 1 IU/ml (range 0.5-1.5 IU/ml) measured 4-6 hours after the Fragmin injection. If the anti-Xa level is below or above the therapeutic range, the dose of Fragmin should be increased or reduced, respectively, by one pre-filled syringe and the anti-Xa measurement should be repeated after 3-4 new doses. This dose adjustment is to be repeated until the anti-Xa therapeutic level is achieved.

  Simultaneous anticoagulant treatment with oral vitamin K-antagonists can be started immediately. Treatment with Fragmin is continued until the prothrombin complex-levels (factor II, VII, IX and X) have dropped to a therapeutic level. Combined treatment during at least five days is usually required.

Method of administration
Subcutaneous administration.

Paediatric population
The safety and efficacy of Fragmin in children have not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Monitoring Anti-Xa levels in children
Measurement of peak anti-Xa levels at about 4 hours post-dose should be considered for certain special populations receiving Fragmin, such as children. For therapeutic treatment with doses administered once daily, peak anti-Xa levels should generally be maintained between 0.5 and 1.0 IU/ml measured at 4 hours post-dose. In the case of low and changing physiologic renal function such as in neonates, close monitoring of anti-Xa levels is warranted. For prophylaxis treatment the anti- Xa levels should generally be maintained between 0.2-0.4 IU/ml.

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.

4.3. Contraindications

The administration of Fragmin is contra-indicated in the following circumstances:
- Hypersensitivity to dalteparin sodium, to any of the excipients listed in section 6.1, to other low-molecular weight heparins, or heparins, or pork products.
- A history of established or suspected immunologically-mediated heparin-induced thrombocytopenia (type II).
- Acute gastroduodenal ulcer.
- Cerebral haemorrhage, or other active haemorrhage.
- Serious coagulation disorders.
- Acute or sub-acute septic endocarditis.
- Injuries to and operations in the central nervous system, eyes and ears.
- Spinal or epidural anaesthesia or spinal puncture is contra-indicated with concomitant treatment with high doses of dalteparin (such as those needed to treat acute deep-vein thrombosis, pulmonary embolism and unstable coronary artery disease) (see section 4.4).
- Fragmin presentations containing benzyl alcohol (Fragmin 10,000 IU (anti-Xa)/ml 10 ml vial and Fragmin 25,000 IU (anti-Xa)/ml 4 ml vial) must not be given to premature babies or neonates. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old (see also sections 4.4 and 4.6).

4.4. Special warnings and 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.

Risk of haemorrhage
Caution is recommended in connection with thrombocytopenia and platelet function disorders, severe liver and renal insufficiency, uncontrolled hypertension, hypertensive or diabetic retinopathy and known hypersensitivity to heparin preparations and/or low-molecular weight heparin preparations. 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) of newly operated patients and other conditions with suspicion of increased risk of haemorrhage.

If a patient with unstable coronary artery disease (unstable angina and non-Q-wave infarction) is struck by myocardial infarction, thrombolytic treatment may be regarded as necessary. It does not mean that the dalteparin treatment must be discontinued, but increases the risk of haemorrhage.

Epidural or spinal anaesthesia
When neuraxial anaesthesia (epidural/spinal anaesthesia) or spinal puncture is employed, associated with the use of low molecular weight heparins, patients (including those who are scheduled to be anticoagulated) 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 after surgery 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 when anticoagulation is given in connection with epidural/spinal anesthesia.

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 the epidural or spinal catheter should be postponed to 10-12 hours after 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. All epidural/spinal anaesthesia or spinal puncture in combination with curative treatment of deep-vein thrombosis is contra-indicated (see sections 4.2 and 4.3). After removal of the catheter, it is necessary to wait for at least 4 hours before the next administration of Fragmin.

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 sign and symptom of neurologic impairment such as back pain, sensory or motor deficits (numbness or weakness in the 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 hematoma are suspected, urgent diagnosis and treatment may include spinal cord decompression.

Prosthetic heart valves
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.

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 in rapidly arising thrombocytopenia and severe thrombocytopenia (< 100,000/µl) associated with positive or unknown results of *in vitro* tests of platelet antibodies in the presence of dalteparin or other low-molecular weight heparins and/or heparins. Prior to initiating a treatment with Fragmin in acute deep vein thrombosis, platelet counts should be determined and regularly followed.

In the event of a thrombocytopenia, treatment should be interrupted (see section 4.3). 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 three weeks.
Important: heparin-induced type II thrombocytopenia should not be confused with early postoperative thrombocytopenia.

Monitoring Anti-Xa levels
Monitoring of the anticoagulant effect of dalteparin is generally not necessary but should be considered for specific patient populations such as paediatrics; 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 APTT (Activated Partial Thromboplastin Time) is only prolonged to a moderate extent by dalteparin, and should not be used because this test is relatively insensitive to the activity of dalteparin. An increase of the dose with the aim to prolong the APTT may therefore be a risk of overdose and haemorrhage (see section 4.9). For laboratory monitoring of effects, functional anti-Xa methods are recommended.

Hyperkalaemia, renal impairment
Heparin, including dalteparin, 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.

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 their therapeutic index is narrower. These patients should have a more comprehensive monitoring of the anti-Xa levels.

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

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. It is therefore important that instructions of use of the respective product are recognised.

Paediatric population
Clinical experience of treatment of children is limited. If dalteparin is used in children the anti-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”, a respiratory disorder characterized by persistent gasp (see section 4.6).

Benzyl alcohol containing formulations must not be used in premature or newborn babies. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old (see section 6.1). Other formulations without benzyl alcohol are available.

Use in geriatric patients
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).

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

Simultaneous medication with effect on the haemostasic functions, such as anti-platelet agents, thrombolytics, acetyl salicylic acid, NSAIDs, GP IIb/IIIa receptor antagonists, vitamin-K antagonists and Dextran may intensify the anticoagulant effect of dalteparin.

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.

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.

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.

Paediatric population
Interaction studies have only been performed 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.

There are more than 2,000 published cases (studies, case series and case reports) on administration of dalteparin during 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 during 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 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).

Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anti-coagulant doses of low molecular weight heparin. Fragmin has not been adequately studied for use in pregnant women with prosthetic heart valves (see section 4.4).

Breastfeeding
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.

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 effects 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 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: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

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
Nervous System Disorders	Not Known*	Intracranial bleeds have been reported and some have been fatal
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 (ASAT, ALAT)
Skin and subcutaneous tissue disorders	Rare	Skin necrosis, transient alopecia
	Not Known*	Rash
General disorders and administration site conditions	Common	Subcutaneous haematoma at the injection site Pain at the injection site
Injury, Poisoning and	Not Known*	Spinal or epidural hematoma (see sections 4.3 and

Procedural Complications		4.4)

*(cannot be established from available data)

The risk of bleeding is depending on the dose. Most bleedings are mild to moderate. 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 according to their local country requirements.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotics. ATC code: B01AB04.

Mechanism of action
Fragmin is an antithrombotic drug containing dalteparin sodium. Dalteparin sodium is a low-molecular weight heparin derived from porcine intestinal mucosa, with an average molecular mass of 6,000 Daltons (range 5,600 – 6,400). The antithrombotic effect of dalteparin sodium is due to its property to enhance the inhibition of factor Xa and thrombin by antithrombin (AT). The potentiating effect of dalteparin sodium on the inhibition of factor Xa is relatively greater compared to its prolonging action on the APTT.

Pharmacodynamic effects
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).

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-Xa levels should be monitored.

The largest prospective study 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 (Nohe et al, 1999).

Nohe et al (1999) Study Demographics and Trial Design

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

5.2. Pharmacokinetic properties

Absorption
Absolute bioavailability in healthy volunteers, measured as anti-Xa activity, was 87 ± 6%. Dose increase from 2500 to 10,000 IU led to a global increase of the anti-Xa AUC that was proportionally higher by about one third.

Distribution
The volume of distribution for the anti-Xa activity of dalteparin was between 40 and 60 ml/kg.

Biotransformation
After administration of IV doses of 40 and 60 IU/kg, mean plasma half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer plasma half-lives (3 to 5 hours) were observed with SC injections; this may be due to delayed absorption.

Elimination
Dalteparin is mainly excreted through the kidneys; however, the biological activity of fragments eliminated renally is not very pronounced. Less than 5% of the anti-Xa activity is detected in the urine. The mean plasma clearance of the anti-Xa activity of dalteparin in healthy volunteers, after administration of single IV bolus injections of 30 IU and 120 IU/kg of anti-Xa, was 24.6 ± 5.4 and 15.6 ± 2.4 ml/h/kg, respectively. The corresponding mean disposition half-lives were 1.47 ± 0.3 and 2.5 ± 0.3 hours.

Haemodialysis
In patients with chronic renal failure requiring haemodialysis, the mean plasma half-life of anti-Xa activity after a single IV dose of 5000 IU dalteparin was 5.7 ± 2.0 hours, which was clearly more than the values observed in healthy volunteers. Therefore, greater accumulation is to 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-Xa activity.

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

The results revealed no organotoxicity, irrespective of method of administration, posology or treatment period. No mutagenic effect was established. No embryotoxic or teratogenic effects were observed; no effects were observed either on fertility or on peri- or postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Fragmin 7,500 IU (anti-Xa)/0.3 ml - Fragmin 10,000 IU (anti-Xa)/0.4 ml - Fragmin 12,500 IU (anti-Xa)/0.5 ml - Fragmin 15,000 IU (anti-Xa)/0.6 ml - Fragmin 18,000 IU (anti-Xa)/0.72 ml: sodium hydroxide, hydrochloric acid, water for injection, nitrogen.

Fragmin 2,500 IU (anti-Xa)/0.2 ml - Fragmin 2,500 IU (anti-Xa)/ml (4 ml vials) - Fragmin 2,500 IU (anti-Xa)/ml (4 ml ampoules) - Fragmin 7,500 IU (anti-Xa)/0.75 ml - Fragmin 10,000 IU (anti-Xa)/ml (1 ml ampoules) - Fragmin 10,000 IU (anti-Xa)/ml (1 ml syringes): sodium chloride, sodium hydroxide, hydrochloric acid, water for injection.

Fragmin 10,000 IU (anti-Xa)/ml (10 ml vial) - Fragmin 25,000 IU (anti-Xa)/ml (4 ml vial): benzyl alcohol, sodium hydroxide, hydrochloric acid, water for injection.
Benzyl alcohol is added as a preservative to the 10,000 IU/ml - 10 ml and 25,000 IU/ml - 4 ml multi-dose vial presentations.

Fragmin 5,000 IU (anti-Xa)/0.2 ml: sodium hydroxide, hydrochloric acid, water for injection.

6.2. Incompatibilities

The solution for injection may be mixed with a physiological NaCl solution (0.9 %) or with isotonic glucose solutions (5 %), in glass or plastic containers. Since the compatibility of Fragmin with other medicines has not been studied so far, Fragmin solution should not be combined with any other medicine.

6.3. Shelf life

Do not use Fragmin after the expiry date which is stated on the Carton label after EXP:. The expiry date refers to the last day of that month.

6.4. Special precautions for storage

Store below 30° C.

Fragmin 10,000 IU (anti-Xa)/ml (10 ml vial) - Fragmin 25,000 IU/ml (4 ml vial): the solution should be used within 14 days after the vial is initially opened.

6.5 Nature and contents of container

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).

- Fragmin 2,500 IU/0.2 ml: 10 pre-filled syringes (with or without Needle-Trap) containing 0.2 ml.
- Fragmin 5,000 IU/0.2 ml: 10 pre-filled syringes (with or without Needle-Trap) containing 0.2 ml.
- Fragmin 7,500 IU/0.3 ml: 10 pre-filled syringes (with or without Needle-Trap) containing 0.3 ml.
- Fragmin 10,000 IU/0.4 ml: 2 or 5 pre-filled syringes (with or without Needle-Trap) containing 0.4 ml.
- Fragmin 12,500 IU/0.5 ml: 2 or 5 pre-filled syringes (with or without Needle-Trap) containing 0.5 ml.
- Fragmin 15,000 IU/0.6 ml: 2 or 5 pre-filled syringes (with or without Needle-Trap) containing 0.6 ml.
- Fragmin 18,000 IU/0.72 ml: 2 or 5 pre-filled syringes (with or without Needle-Trap) containing 0.72 ml.

Graduated pre-filled syringes
- Fragmin 7,500 IU/0.75 ml: 10 graduated pre-filled syringes containing 0.75 ml.
- Fragmin 10,000 IU/ml: 10 graduated pre-filled syringes containing 1 ml.

Vials
- Fragmin 2,500 IU/ml: 10 vials containing 4 ml (=10,000 IU/4 ml).
- Fragmin 10,000 IU/ml: 1 vial containing 10 ml (=100,000 IU/10 ml).
- Fragmin 25,000 IU/ml: 1 vial containing 4 ml (=100,000 IU/4 ml).

Ampoules
- Fragmin 2,500 IU/ml: 10 ampoules containing 4 ml (=10,000 IU/4 ml).
- Fragmin 10,000 IU/ml: 10 ampoules containing 1 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Using the pre-filled syringe with the Needle-Trap feature
Administer as per the standard protocol.

Following administration
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 feature. The Needle-Trap is designed to specifically help prevent accidental needle sticks following the proper administration of injectable medications.

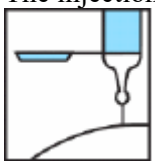
The Needle-Trap requires specific actions by the user to “activate” the Needle-Trap, which will render the needle harmless after the injection is administered.

The Needle-Trap is attached to the syringe barrel and the plastic portion (catcher) extends towards the tip of the needle cover aligned parallel to the needle/needle cover.

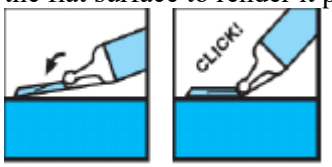
The user grasps the tip of the plastic needle catcher and bends it away from needle shield.

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.

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

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

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MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

October 2020