Fragmin 10000 IU/1 ml solution for injection

Summary of Product Characteristics Updated 23-Feb-2023 | Pfizer Limited

▼ 1. Name of the medicinal product

Fragmin 10,000 IU/1 ml

▼ 2. Qualitative and quantitative composition

Active ingredient

Dalteparin sodium (INN)

Quality according to Ph Eur and in-house specification.

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

Content of active ingredient

Ampoules containing dalteparin sodium, 10,000 IU (anti-Factor Xa) in 1 ml.

For the full list of excipients, see section 6.1.

▼ 3. Pharmaceutical form

Solution for injection for intravenous or subcutaneous administration.

▼ 4. Clinical particulars
▼ 4.1 Therapeutic indications

Prevention of clotting in the extracorporeal circulation during haemodialysis or haemofiltration, in patients with chronic renal insufficiency or acute renal failure.

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

Unstable angina and non-Q wave myocardial infarction (unstable coronary artery disease-UCAD), administered concurrently with aspirin.

Extended Use

Fragmin may be used beyond 8 days in patients awaiting angiography/ revascularisation procedures (see Section 5.1)

Paediatric population

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

▼ 4.2 Posology and method of administration

Recommended dosage for adults

(i) Prevention of clotting during haemodialysis and haemofiltration

Administer Fragmin into the arterial side of the dialyzer or intravenously.

In chronic renal insufficiency for patients with no known additional bleeding risk, the dosage is:

(a) Long-term haemodialysis or haemofiltration - duration of haemodialysis/haemofiltration more than 4 hours;

An I.V. bolus injection of Fragmin 30-40 IU (anti-Factor Xa)/kg bodyweight, followed by an infusion of 10-15 IU (anti-Factor Xa)/kg bodyweight/hour.

(b) Short-term haemodialysis or haemofiltration - duration of haemodialysis/haemofiltration less than 4 hours:

A single bolus injection of 5000 IU can be administered, either intravenously or into the arterial side of the extracorporeal system, at the start of the procedure. Alternatively, an I.V. bolus injection of Fragmin 30-40 IU (anti-Factor Xa)/kg bodyweight, followed by an infusion of 10-15 IU (anti-Factor Xa)/kg bodyweight/hour.

The 5000 IU starting dose for the single bolus dosing regimen can be adjusted, session-to-session, based on the outcome of the previous dialysis; the dose may be increased or decreased in steps of 500 or 1000 anti-Xa IU (according to clinical judgement) until a satisfactory outcome is obtained (see section 5.1.).

In acute renal failure, or chronic renal failure in patients with a high risk of bleeding, the dosage is:

An I.V. bolus injection of Fragmin 5-10 IU (anti-Factor Xa)/kg bodyweight, followed by an infusion of 4-5 IU (anti-Factor Xa)/kg bodyweight/hour.

The plasma anti-Factor Xa levels should be within the range 0.2-0.4 IU (anti-Factor Xa)/ml.

When considered necessary, it is recommended that the antithrombotic effect of Fragmin be monitored by analysing anti-Factor Xa activity using a suitable chromogenic substrate assay. This is because Fragmin has only a moderate prolonging effect on clotting time assays such as APTT or thrombin time.

(ii) Treatment of venous thromboembolism (VTE)

Fragmin can be administered subcutaneously either as a single daily injection or as twice daily injections.

(a) Once daily administration

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

(b) Twice daily administration

A dose of 100 IU/kg body weight administered sc. twice daily can be used for patients with increased risk of bleeding. Monitoring of the treatment is generally not necessary but can be performed with a functional anti-Factor Xa assay. Maximum plasma levels are obtained 3-4 hours after sc. injection, when samples should be taken. Recommended plasma levels are between 0.5-1.0 IU (anti-Factor Xa)/ml.

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

(iii) Unstable coronary artery disease

120 IU/kg body weight are administered subcutaneously twelve hourly for up to 8 days if considered of benefit by the physician. The maximum dose is 10,000 IU/12 hours

Patients needing treatment beyond 8 days, while awaiting angiography/revascularisation, should receive a fixed dose of either 5,000 IU (women < 80 kg and men <70 kg) or 7,500 IU (women ≥ 80 kg and men ≥ 70 kg) 12 hourly. Treatment is recommended to be given until the day of the revascularisation procedure (PTCA or CA BG) but not for more than 45 days.

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.

Table 1 - 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

Table 2 – 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.

* 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.

** 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.

*** 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

Fragmin is administered by subcutaneous injection for all indications except for the prevention of clotting in the extracorporeal system during haemodialysis and haemofiltration where it is administered either intravenously or into the arterial side of the dialyzer.

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 disorder; acute or sub-acute septic endocarditis; 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).

▼ 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 interactions section). 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).

It is recommended that platelets be counted before starting treatment with Fragmin and monitored regularly. Special caution is necessary in rapidly developing thrombocytopenia and severe thrombocytopenia (<100,000/µ l) 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 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 µ mol/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.

Excipients

Sodium

Fragmin 10,000 IU (anti-Xa)/1 ml contains less than 1 mmol (23 mg) of sodium per ampoule, 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

The possibility of the following interactions with Fragmin should be considered:

(i) An enhancement of the anticoagulant effect by anticoagulant/antiplatelet agents e.g. aspirin/ dipyridamole, GP IIb/IIIa receptor antagonists, vitamin K antagonists, NSAIDs e.g. indomethacin, cytostatics, dextran, thrombolytics, sulphinpyrazone, probenecid, and ethacrynic acid.

(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 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 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.

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
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 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%. 1 mg of protamine inhibits the effect of 100 IU (anti-Factor Xa) of Fragmin.

▼ 5. Pharmacological properties

▼ 5.1 Pharmacodynamic properties

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. 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

In a prospectively randomised study in 3489 patients (FRISC II) with acute coronary syndromes, early invasive strategy was clearly superior to non – invasive strategy.

In a post-hoc analysis, the extended use of Fragmin, up to Day 45 reduced the incidence of death and/or MI compared with placebo in the non-invasive group (revascularisation only if necessary).

The use of Fragmin beyond 8 days did not significantly reduce the incidence of death and/or MI, compared to placebo, in patients who were contraindicated to early angiography and revascularisation.

Parrot Study (A6301091): A phase IIIb open-label study in adults aged 18 to 85 years that allowed flexible dosing with increment/decrement of 500 or 1000 IU following standard dalteparin sodium 5000 IU bolus to optimize treatment for the prevention of clotting within the extracorporeal system during haemodialysis procedures for subjects with chronic renal insufficiency.

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

Study Demographics and Trial Design

Diagnosis	**Dalteparin Dosage, Route of Administration and Duration**	**Study subjects**
Subjects with end stage renal failure requiring 3 or 4 haemodialysis sessions (for 4 hours or less) per week, with no other known risks of bleeding.	5000 IU single bolus dose given into the arterial side of the dialyzer at the start of the procedure. This dose could be adjusted by increment/decrement of 500 IU or 1000 IU, at the discretion of the investigator. Criteria for dose adjustments were occurrence of clotting grade 3 or 4, minor bleeding during haemodialysis or between haemodialysis sessions, prolonged access compression time (>10 minutes) or other clinical events. Study duration for a maximum of 20 haemodialysis sessions	152 subjects enrolled and treated Gender: 106 males, 46 females

The mean proportion of successful haemodialysis sessions (defined as a haemodialysis session which was completed as planned, without the need for premature termination due to clotting in the haemodialysis circuit) was 99.9% (2774 of 2776 evaluable haemodialysis sessions; 50 haemodialysis sessions were

excluded from the analysis because the effect of dalteparin sodium could not be assessed), with a 95% CI of 99.7% to 100.0%. No haemodialysis session was prematurely terminated due to a safety event of bleeding.

For subjects who completed at least one haemodialysis session, the dalteparin dose was adjusted for 79 (52.3%) subjects, and 72 (47.7%) subjects received the standard fixed dose of 5000 IU per haemodialysis session at all haemodialysis sessions.

There was no evidence of bioaccumulation of anti-Xa serum levels. Only for 2 subjects, the pre-haemodialysis session value was above the threshold of <0.4 IU/mL at haemodialysis 10 but this was resolved at haemodialysis session 20.

The results of this study demonstrate that a flexible dosing regimen of dalteparin sodium administered into the arterial side of the extracorporeal system during haemodialysis sessions up to 4 hours in subjects with chronic renal failure and no other known risks of bleeding is effective and well tolerated, and that a flexible dosing regimen is appropriate to address the potential limitations of the fixed dose regimen (5000 IU).

Overall, an adjustable dalteparin sodium dose regimen allowed safe completion of haemodialysis, with clinical benefits over fixed dosing.

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 3 - 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 iv and sc. administration is 2 hours and 3.5-4 hours respectively, twice that of unfractionated heparin.

Bioavailability

The bioavailability following sc. 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 through 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 4 - 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 did not have a greater osteopenic effect than heparin since at equivalent doses the osteopenic effect was comparable.

The results revealed no organ toxicity irrespective of the route of administration, doses or the 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

Sodium chloride (Ph Eur)

Water for injections (Ph Eur)

▼ 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.

Fragmin 10,000 IU/1 ml ampoule diluted with sodium chloride (9 mg/ml) or glucose (50 mg/ml) to a concentration of 2,500 IU/ml: chemical and physical stability has been demonstrated for 24 hours at 20° C when stored in a polypropylene syringe or glass vial.

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 30° C.

▼ 6.5 Nature and contents of container

Clear glass ampoules (Ph Eur Type 1) containing dalteparin sodium, 10,000 IU (anti-factor Xa) in 1 ml

▼ 6.6 Special precautions for disposal and other handling

Fragmin solution for injection is compatible with sodium chloride (9 mg/ml) or glucose (50 mg/ml) infusion solutions in glass bottles and plastic containers for up to 24 hours. Compatibility between Fragmin and other products has not been studied.

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

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▼ 8. Marketing authorisation number(s)

PL 00057/977

▼ 9. Date of first authorisation/renewal of the authorisation

5 April 2002/30 July 2007

▼ 10. Date of revision of the text

02/2023

Ref: FR 9_2

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