Dalteparin Sodium Solution for Injection FRAGMIN®

1. GENERIC NAME

Dalteparin Sodium Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Dalteparin Sodium Ph.Eur.

- Single dose syringe 2,500 IU (anti-Factor Xa)/0.2 ml,
- Single dose syringe 5,000 IU (anti-Factor Xa)/0.2 ml ,
- Multi-dose vial of 10,000 IU (anti-Factor Xa)/ml, in 10 ml.

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

List of Excipients

Single dose syringe of 2,500 IU : Sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

Single dose syringe of 5,000 IU : Sodium hydroxide, hydrochloric acid and water for injection.

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

Not all strengths/presentations mentioned in this document may be available in the market.

Excipients with known effect

Benzyl alcohol

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml vial) contains 140 mg of benzyl alcohol in each vial, which is equivalent to 14 mg/ml of benzyl alcohol.

Sodium

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml vial) contains 113.6 mg sodium per vial.

3. DOSAGE FORM AND STRENGTH

Sterile solution for subcutaneous and intravenous administration.
Single dose syringe 2,500 IU (anti-Factor Xa)/0.2 ml, Single dose syringe 5,000 IU (anti-Factor Xa)/0.2 ml and Multi-dose vial of 10,000 IU (anti-Factor Xa)/ml, in 10 ml.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Treatment of acute deep-vein thrombosis.

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

3. Thromboprophylaxis in conjunction with surgery.

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

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

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

4.2 Posology and Method of Administration

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

General - DO NOT ADMINISTER FRAGMIN SOLUTION FOR INJECTION BY THE INTRAMUSCULAR ROUTE.

FRAGMIN Solution for Injection 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.

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

1. <u>Treatment of Acute Deep-vein Thrombosis</u>

Administer FRAGMIN Solution for Injection subcutaneously (SC) either as a single daily injection or as two daily injections. Simultaneous anticoagulation with oral vitamin-K antagonists can be started immediately. Continue combined treatment until the prothrombin complex tests have reached therapeutic levels (usually at least 5 days). Outpatient treatment is feasible using the same doses recommended for treatment in a medical institution.

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

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

2. <u>Prevention of Clotting in the Extra-corporeal System during Haemodialysis and Haemofiltration</u>

Administer FRAGMIN Solution for Injection into the arterial side of the dialyzer or intravenously, selecting the appropriate regimen from those described below.

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

    - **Haemodialysis and haemofiltration up to a maximum of 4 hours -** A single bolus injection of 5,000 IU can be administered, either intravenously or into the arterial side of the extracorporeal system, at the start of the procedure. Alternatively, administer 30 to 40 IU/kg total body weight IV bolus injection, followed by 10 to 15 IU/kg/h IV infusion.

      The 5,000 IU starting dose for the single bolus dosing regimen can be adjusted, session-to-session, based on the outcome of the previous dialysis; the dose may be increased or decreased in steps of 500 or 1,000 anti-Factor Xa IU until a satisfactory outcome is obtained (see section 5.2 **Pharmacodynamic Properties**).

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

- **Patients with acute renal failure, or patients with a high risk of bleeding -** Administer 5 to 10 IU/kg total body weight as IV bolus injection, followed by 4 to 5 IU/kg/h IV infusion. Patients undergoing acute haemodialysis have a narrower therapeutic range than patients on chronic haemodialysis, and should undergo comprehensive monitoring of

anti-Factor Xa levels. Recommended plasma levels are between 0.2 and 0.4 IU anti-Factor Xa/ml.

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

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

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

- **Patients at risk for thromboembolic complications -** 2,500 IU SC within 2 hours before surgery and 2,500 IU SC each post-operative morning until the patient is mobilized (generally 5 to 7 days or longer).

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

    - **Start on day before surgery:** 5,000 IU SC on the evening before surgery. Following surgery, 5,000 IU SC each evening.

    - **Start on day of surgery:** 2,500 IU SC within 2 hours before surgery and 2,500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5,000 IU SC each morning.

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

    - **Preoperative start - Evening before surgery:** 5,000 IU SC on the evening before surgery. Following surgery, 5,000 IU SC each evening.

    - **Preoperative start - Day of surgery:** 2,500 IU SC within 2 hours before surgery and 2,500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5,000 IU SC each morning.

    - **Post-operative start:** 2,500 IU SC 4 to 8 hours after surgery, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5,000 IU SC each day.

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

Administer 5,000 IU of FRAGMIN Solution for Injection subcutaneously (SC) once daily,

generally for 12 to 14 days or longer in patients with continued restricted mobility. Monitoring of the anticoagulant effect is generally not necessary.

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

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

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

- For women weighing less than 80 kg and men weighing less than 70 kg, administer 5,000 IU SC every 12 hours.
- For women weighing at least 80 kg and men weighing at least 70 kg, administer 7,500 IU SC every 12 hours.

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

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

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

Month 1

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

Months 2 to 6

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

Table 2 Dose of FRAGMIN Solution for Injection to be Administered Subcutaneously by Patient Weight during Months 2-6		
Body Weight (lbs)	**Body Weight (kg)**	**FRAGMIN Solution for Injection Dose (IU) (prefilled syringe) once daily**
≤124	≤56	7,500
125 to 150	57 to 68	10,000
151 to 181	69 to 82	12,500
182 to 216	83 to 98	15,000
≥217	≥99	18,000

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

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

Dose reductions for renal insufficiency in extended treatment of acute symptomatic venous thromboembolism in patients with cancer - In patients with severely impaired renal

function (CrCl <30 ml/min), monitoring for anti-Factor Xa levels is recommended to determine the appropriate FRAGMIN Solution for Injection dose. Target anti-Factor Xa is 0.5-1.5 IU/ml. When monitoring anti-Factor Xa in these patients, sampling should be performed 4-6 hrs after FRAGMIN Solution for Injection dosing and only after the patient has received 3-4 doses.

4.3 Contraindications

FRAGMIN Solution for Injection should not be used in patients who have the following:

- Established or suspected history of immunologically-mediated heparin-induced thrombocytopenia (type II).
- Active, clinically-significant bleeding (such as gastrointestinal ulceration or bleeding, or cerebral haemorrhage).
- Serious coagulation disorders.
- Septic endocarditis.
- Injuries to and operations in the central nervous system, eyes and/or ears.
- Hypersensitivity to dalteparin, or other low-molecular weight heparins, or heparins, or pork products.
- Because of an increased risk of bleeding, high doses of FRAGMIN Solution for Injection (such as those needed to treat acute deep-vein thrombosis, pulmonary embolism, and unstable coronary artery disease) should not be used in patients who will receive spinal or epidural anaesthesia or other procedures requiring spinal puncture (see section 4.4 **Special Warnings and Precautions for Use**).

4.4 Special Warnings and Precautions for Use

FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection (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 FRAGMIN Solution for Injection treatment must be discontinued, but increases the risk of haemorrhage.

The concomitant use with drugs affecting hemostasis, such as thrombolytic agents, other anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or dextran may enhance the anticoagulant effect of FRAGMIN Solution for Injection and is not recommended. Appropriate caution should be exercised under specific circumstances of switching anticoagulant therapy (see section 4.5 **Drugs Interactions**).

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 anaesthesia.

In order to reduce the risk of bleeding associated with the use of FRAGMIN Solution for Injection during spinal or epidural anaesthesia, it is preferable to insert or remove the catheter when the anticoagulant effect of FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection 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 contraindicated (see sections 4.2 **Posology and Method of Administration** and 4.3 **Contraindications**). After removal of the catheter, it is necessary to wait for at least 4 hours before the next administration of FRAGMIN Solution for Injection.

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 Solution for Injection in preventing valve thrombosis in patients with prosthetic heart valves. Prophylactic doses of FRAGMIN Solution for Injection are not sufficient to prevent valve thrombosis in patients with prosthetic heart valves. The use of FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection or other low-molecular weight heparins and/or heparins. Prior to initiating a treatment with FRAGMIN Solution for Injection 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 **Contraindications**). Treatment should then be started with a fractionated heparin that did not cause aggregation with the platelets of the patient in an *in-vitro* aggregation test. Subsequently, platelet count should be performed at least twice a week, in particular during the first three weeks.

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

Monitoring Anti-Factor Xa levels

Monitoring of the anticoagulant effect of FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection , and should not be used because this test is relatively insensitive to the activity of FRAGMIN Solution for Injection. 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 **Overdose**). For laboratory monitoring of effects, functional anti-Factor 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 undergoing acute haemodialysis may be more unstable and their therapeutic index is narrower. These patients should have monitoring of the anti-Factor 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 Patients

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

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 FRAGMIN Solution for Injection.

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

Benzyl Alcohol

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml vial) presentation contains benzyl alcohol. Formulations of FRAGMIN Solution for Injection without benzyl alcohol are available (see section 2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**).

The preservative benzyl alcohol may cause hypersensitivity reactions. Intravenous

administration of benzyl alcohol has been associated with serious adverse events and death in paediatric patients including neonates ("gasping syndrome"). Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome" the minimum amount of benzyl alcohol at which toxicity may occur is not known.

Benzyl alcohol containing formulations should only be used in premature or newborn babies if it is necessary and if there are no alternatives possible. Premature and low birth weight neonates may be more likely to develop toxicity. Benzyl alcohol containing formulations should not be used for more than 1 week in children under 3 years of age unless necessary.

If use of a benzyl alcohol containing formulation of FRAGMIN Solution for Injection is necessary, it is important to consider the combined daily metabolic load of benzyl alcohol from all sources, especially in patients with liver or kidney impairment, as well as in pregnant or breast-feeding women, because of the risk of accumulation and toxicity (metabolic acidosis).

Sodium

FRAGMIN Solution for Injection 2,500 IU/0.2 ml, FRAGMIN Solution for Injection 5,000 IU (anti-Factor Xa)/0.2 ml, contain 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 Solution for Injection can be informed that these medicinal product formulations are essentially "sodium free".

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml vial) contains 113.6 mg sodium per vial, equivalent to 5.68% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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.

Allergic Reactions

The needle shield of FRAGMIN Solution for Injection prefilled syringes may contain latex (natural rubber) which may cause severe allergic reactions in individuals with hypersensitivity to latex (natural rubber).

4.5 Drugs Interactions

Drugs increasing effects of FRAGMIN Solution for Injection
Simultaneous medication with effect on the haemostatic functions, such as other anticoagulants, anti-platelet agents, thrombolytic, acetyl salicylic acid, NSAIDs, GP IIb/IIIa receptor antagonists, vitamin-K antagonists and dextran, may intensify the anticoagulant effect of FRAGMIN Solution for Injection (see section 4.4 **Special Warnings and Precautions for Use**).

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 FRAGMIN Solution for Injection concomitantly with NSAIDs or high dose ASA in patients with renal failure.

Drugs antagonizing effects of FRAGMIN Solution for Injection
The concomitant use of FRAGMIN Solution for Injection with andexanet alfa may reduce the effectiveness of FRAGMIN Solution for Injection. 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 FRAGMIN Solution for Injection.

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 FRAGMIN Solution for Injection .

4.6 Use in Special Populations

Pregnancy

FRAGMIN Solution for Injection 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. dalteparin 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 FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection (see section 6.1 **Animal Toxicology or Pharmacology**).

Epidural anaesthesia during childbirth is absolutely contraindicated in women who are being treated with high-dose anticoagulants (see section 4.3 **Contraindications**). Caution is recommended when treating patients with an increased risk of haemorrhage, such as perinatal women (see section 4.4 **Special Warnings and Precautions for Use**). In pregnant women

during the last trimester, FRAGMIN Solution for Injection anti-Factor Xa half-lives of 4 to 5 hours were measured.

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml vial) presentation contains benzyl alcohol as a preservative. As benzyl alcohol may cross the placenta, FRAGMIN Solution for Injection without preservative should be used during pregnancy (see section 4.4 **Special Warnings and Precautions for Use**).

Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anti-coagulant doses of low molecular weight heparin. FRAGMIN Solution for Injection has not been adequately studied for use in pregnant women with prosthetic heart valves.

Breast-feeding

Small amounts of FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection). 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 Solution for Injection should be made taking into account the benefit of breast-feeding to the child and the benefit of FRAGMIN Solution for Injection therapy to the woman.

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml vial) presentation contains benzyl alcohol as a preservative. As benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant, FRAGMIN Solution for Injection without preservative should be used during breast-feeding (see section 4.4 **Special Warnings and Precautions for Use**).

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

4.7 Effects on Ability to Drive and Use Machines

FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection, 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 Procedural Complications	Not Known*	Spinal or epidural hematoma (see sections 4.3 **Contraindications** and 4.4 **Special Warnings and Precautions for Use**)

*(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 **Special Warnings and Precautions for Use**).

Long-term treatment with heparin has been associated with a risk of osteoporosis. Although this has not been observed with FRAGMIN Solution for Injection, 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 FRAGMIN Solution for Injection 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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Pharmacotherapeutic group: antithrombotics. ATC code: B01AB04.

FRAGMIN Solution for Injection is an antithrombotic drug containing dalteparin sodium. Dalteparin is a low-molecular weight heparin derived from porcine intestinal mucosa, with an average molecular weight of 6,000 Daltons (range between 5,600 and 6,400 Daltons). The antithrombotic effect of FRAGMIN Solution for Injection is due to its property to enhance the inhibition of Factor Xa and thrombin by antithrombin (AT). The potentiating effect of FRAGMIN Solution for Injection on the inhibition of Factor Xa is relatively greater compared to its prolonging action on the, e.g., activated partial thromboplastin time (APTT).

5.2 Pharmacodynamic Properties

FRAGMIN Solution for Injection 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 FRAGMIN Solution for Injection 5,000 IU once daily was compared to unfractionated heparin (UFH) 5,000 IU twice daily in 3,746 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 FRAGMIN Solution for Injection (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).

Parrot Study (A6301091): A phase IIIb open-label study in adults aged 18 to 85 years to optimize treatment for the prevention of clotting within the extracorporeal system during haemodialysis procedures for subjects with chronic renal insufficiency.

Table 4
Study Demographics and Trial Design

Diagnosis	**FRAGMIN Solution for Injection 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.	5,000 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 1,000 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% (2,774 of 2,776 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 FRAGMIN Solution for Injection dose was adjusted for 79 (52.3%) subjects, and 72 (47.7%) subjects received the standard fixed dose of 5,000 IU per haemodialysis session at all haemodialysis sessions.

There was no evidence of bioaccumulation of anti-Factor 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.

Prophylaxis of venous thromboembolism in Paediatric Population

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

5.3 Pharmacokinetic Properties

Absorption –
Absolute bioavailability in healthy volunteers, measured as the anti-Factor Xa activity, was 87 ± 6%. Increasing the dose from 2,500 to 10,000 IU resulted in an overall increase in anti-Factor Xa AUC that was proportionally greater by about one-third.

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

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

Excretion –
FRAGMIN Solution for Injection is primarily excreted by the kidneys, however, the biological activity of fragments eliminated renally is not well pronounced. Less than 5% of anti-Factor Xa activity is detectable in the urine. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single intravenous bolus doses of 30 and 120 anti-

Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 ml/h/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 and 2.5 ± 0.3 hours.

Special Populations

Haemodialysis - In patients with chronic renal failure requiring haemodialysis, the mean plasma half-life of anti-Factor Xa activity following a single IV dose of 5,000 IU FRAGMIN Solution for Injection 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 5. 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 5 Pharmacokinetic Parameters of FRAGMIN Solution for Injection 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) $t_{½β}$ (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; $t_{½β}$=elimination half-life; V_d=volume of distribution.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

The acute toxicity of FRAGMIN Solution for Injection is significantly lower compared to that of heparin.

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

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

The osteoporosis effect of FRAGMIN Solution for Injection does not exceed that of heparin.

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

7. DESCRIPTION

Solution for injection 2,500 IU (anti-Factor Xa)/0.2 ml, single dose syringes 10 x 0.2 ml
A clear, colorless or straw-colored solution.

Solution for injection 5,000 IU (anti-Factor Xa)/0.2 ml, single dose syringes 10 x 0.2 ml
A clear, colorless or straw-colored solution.

1 multidose vial of 10 ml containing 10,000 IU (anti-Factor Xa)/ml
A clear, colorless or straw-colored solution.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Compatibility between FRAGMIN Solution for Injection and products other than those mentioned under (section 4.2 **Posology and Method of Administration)** has not been investigated.

8.2 Shelf-life

36 months

8.3 Packaging Information

How supplied

Solution for injection 2,500 IU (anti-Factor Xa)/0.2 ml, single dose syringes 10 x 0.2 ml
Solution for injection 5,000 IU (anti-Factor Xa)/0.2 ml, single dose syringes 10 x 0.2 ml

1 multidose vial of 10 ml containing 10,000 IU (anti-Factor Xa)/ml and 140 mg of benzyl alcohol as preservative.

Pre-filled syringes (with or without Needle-Trap)

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

Not all presentations may be available in the market.

8.4 Storage and Handling Instructions

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

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

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

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

Using the Vials and the Pre-filled Syringes

No special requirements.

Use as per the standard protocol.

9. PATIENT COUNSELLING INFORMATION

Risk of Hemorrhage including Spinal/Epidural Hematomas

If patients have had neuraxial anaesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs, platelet inhibitors, or other anticoagulants, inform the patients to watch for signs and symptoms of spinal or epidural hematoma, such as tingling, numbness (especially in the lower limbs) and muscular weakness. If any of these symptoms occur the patient should contact his or her physician immediately.

Additionally, the use of aspirin and other NSAIDs may enhance the risk of haemorrhage. Discontinue their use prior to FRAGMIN Solution for Injection therapy whenever possible; if co-administration is essential, the patient's clinical and laboratory status should be closely monitored (see section 4.5 **Drug Interactions)**.

Inform Patients:

- of the instructions for injecting FRAGMIN Solution for Injection if their therapy is to continue after discharge from the hospitals.

- it may take them longer than usual to stop bleeding.

- they may bruise and/or bleed more easily when they are treated with dalteparin.

- they should report any unusual bleeding, bruising, or signs of thrombocytopenia (such as a rash of dark red spots under the skin) to their physician (see section 4.4 **Special Warnings and Precautions for Use**).

- to tell their physicians and dentists they are taking FRAGMIN Solution for Injection and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken (see section 4.4 **Special Warnings and Precautions for Use**).

- to tell their physicians and dentists of all medications they are taking, including those obtained without a prescription, such as aspirin or other NSAIDs (see section 4.4 **Special Warnings and Precautions for Use**).

- risks are associated with benzyl alcohol in neonates, infants, and pregnant women (see sections 4.4 **Special Warnings and Precautions for Use** and 4.6 **Use in Special Populations**).

- to tell their physicians and care givers if they are allergic to natural rubber latex (see section 4.4 **Special Warnings and Precautions for Use**).

10. DETAILS OF MANUFACTURER

M/s. Pfizer Manufacturing Belgium NV Rijksweg 12, B-2870 Puurs-Sint-Amands, Belgium

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

FF-362-12005 dated 06 February 2023

12. DATE OF REVISION

August 2025