FULL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

FRAGMIN® 2500 IU /0.2 ML
FRAGMIN® 2500 IU/ML
FRAGMIN® 10000 IU/ML
FRAGMIN® 25000 IU/ML

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Dalteparin sodium

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

Each single dose syringe contains either: 2,500 IU (anti-Factor Xa)/ 0.2 ml; 5000 IU (anti-Factor Xa)/ 0.2 ml 7,500 IU (anti-Factor Xa)/ 0.3 mL,10,000 IU(anti-Factor Xa)/ 0.4mL, 12,500 IU(anti-Factor Xa)/ 0.5 mL, 15,000 IU(anti-Factor Xa)/ 0.6 mL or 18,000 IU(anti-Factor Xa)/ 0.72 mL

Each ampoule contains either: 2,500 IU (anti- Factor Xa)/ml (4ml) or 10,000 IU (anti-Xa)/ml (1ml)

For the full list of excipients, *see Description (11)* in this leaflet.

PHARMACEUTICAL FORM

Solution for injection for subcutaneous or intravenous administration.

WARNING: SPINAL/EPIDURAL HEMATOMAS

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH) or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **Use of indwelling epidural catheters**
- **Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants.**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery**
- **Optimal timing between the administration of FRAGMIN and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [*see Warnings and Precautions (5.1) and Drug Interactions (7)*].

1 THERAPEUTIC INDICATIONS

- Treatment of acute deep venous thrombosis and/or pulmonary embolism.

- Prevention of clotting during hemodialysis and hemofiltration in connection with acute renal failure or chronic renal insufficiency.
- Thromboprophylaxis in conjunction with surgery.
- Unstable coronary artery disease.
- Prophylaxis in patients with substantially increased risk for venous thromboembolism and that are temporarily immobilized due to acute illness such as cardiac insufficiency, respiratory insufficiency and severe infections.
- Cancer patients: Treatment and secondary prevention of deep-vein thrombosis and/or pulmonary embolism.

2 DOSAGE AND ADMINISTRATION

General
DO NOT ADMINISTER DALTEPARIN BY THE INTRAMUSCULAR ROUTE.

2.1 Recommended Dosage

Treatment of Acute Deep Venous Thrombosis and Pulmonary Embolism

FRAGMIN can be administered subcutaneously either as a single daily injection or as two daily injections.

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 18000 IU.

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 Warnings and Precautions (5.1)*]**.**

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-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.
Outpatient treatment is feasible using the same doses recommended for treatment in a medical institution.

Prevention of Clotting During Haemodialysis and Haemofiltration

Administer dalteparin intravenously (IV), selecting the appropriate regimen from those described below.

- Patients with Chronic renal insufficiency or patients with no known risk of bleeding:
  These patients normally require few dose adjustments, and therefore frequent monitoring of anti-Xa levels is not necessary for most patients. Recommended doses usually produce plasma levels between 0.5 to 1.0 IU anti-Xa/mL during dialysis.

- Hemodialysis and hemofiltration up to a maximum of 4 hours:
  Either 30 to 40 IU/kg total body weight IV bolus injection followed by 10 to 15 IU/kg/hour IV infusion, or a single IV bolus injection of 5000 IU.

- Hemodialysis and hemofiltration longer than 4 hours:
  Administer 30 to 40 IU/kg total body weight IV bolus injection, followed by 10 to 15 IU/kg/hour IV infusion.

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

Thromboprophylaxis in Conjunction with Surgery

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

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

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

- Patients with additional risk factors for thromboembolism (e.g., malignancy):
  Administer dalteparin until the patient is mobilized (generally 5 to 7 days or longer).
  - **Start on day before surgery** - 5000 IU SC on the evening before surgery.
  Following surgery, 5000 IU SC each evening.
  - **Start on day of surgery** - 2500 IU SC within 2 hours before surgery and 2500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each morning.

- Orthopedic surgery (such as hip replacement surgery):
  Administer dalteparin for up to 5 weeks after surgery, selecting one of the regimens listed below.
  - **Preoperative start: Evening before surgery** - 5000 IU SC on the evening before surgery. Following surgery, 5000 IU SC each evening.
  - **Preoperative start: Day of surgery** - 2500 IU SC within 2 hours before surgery and 2500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each morning.
  - **Postoperative start -** 2500 IU SC 4 to 8 hours after surgery, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each day.

Thromboprophylaxis in Patients with Restricted Mobility

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

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

Administer dalteparin 120 IU/kg total body weight subcutaneously (SC) every 12 hours up to a maximum dose of 10,000 IU/12 hours. Unless specifically contraindicated, patients should also receive concomitant therapy with acetylsalicylic acid (75 to 325 mg/day). Continue treatment until the patient is clinically stable (generally at least 6 days), or longer if considered of benefit by the physician.

Thereafter, extended treatment with a fixed dose of dalteparin is recommended until a revascularization procedure is performed (such as percutaneous interventions [PCI] or coronary artery bypass graft [CABG]). The total treatment period should not exceed 45 days.

The dose of dalteparin is selected according to the patient's gender and weight:
- For women weighing less than 80 kg and men weighing less than 70 kg, administer 5000 IU SC every 12 hours.
- For women weighing at least 80 kg and men weighing at least 70 kg, administer 7500 IU SC every 12 hours.

Monitoring of the anticoagulant effect is generally not necessary but should be considered for specific patient populations [*See Warnings and Precautions (5.1)*].
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-Xa/mL.

Extended treatment of symptomatic VTE to reduce recurrence of VTE in patients with cancer

- **Month 1**

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

- **Months 2-6**

Dalteparin should be administered at a dose of approximately 150 IU/kg subcutaneously, once daily using fixed dose syringes and Table 1 shown below.

Table 1: Dosage determination for months 2-6

Body Weight (kg)	Dalteparin Dose (IU)
≤56	7500
57 to 68	10,000
69 to 82	12,500
83 to 98	15,000
≥99	18,000

2.2 Dose reductions for chemotherapy-induced thrombocytopenia

Thrombocytopenia

In the case of chemotherapy-induced thrombocytopenia with platelet counts <50,000/mm3, dalteparin should be interrupted until the platelet count recovers above 50,000/mm3.

For platelet counts between 50,000 and 100,000/mm3, dalteparin should be reduced by 17% to 33% of the initial dose depending on the patient's weight (Table 2). Once the platelet count recovered to ≥100,000/mm3, dalteparin should be re-instituted at full dose.

Table 2: Dose Reduction of Dalteparin for Thrombocytopenia 50,000-100,000/mm3

Body Weight (kg)	Scheduled Dalteparin Dose (IU)	Reduced Dalteparin Dose (IU)	Mean Dose Reduction (%)
≤56	7500	5000	33
57 to 68	10,000	7500	25
69 to 82	12,500	10,000	20
83 to 98	15,000	12,500	17
≥99	18,000	15,000	17

Body Weight (kg)	Scheduled Dalteparin Dose (IU)	Reduced Dalteparin Dose (IU)	Mean Dose Reduction (%)

2.3 Renal failure

In the case of significant renal failure, defined as a creatinine level >3 x ULN, the dose of dalteparin 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 dalteparin injection. If the anti-Xa level is below or above the therapeutic range, the dose of dalteparin should be increased or reduced, respectively, by one syringe formulation 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.

2.4 Compatibility

FRAGMIN is compatible with isotonic sodium chloride (9 mg/ml) or isotonic glucose (50 mg/ml) infusion solution in glass bottles and plastic containers. The solution should be used within 12 hours.
Compatibility between FRAGMIN and other products has not been investigated.

2.5 Administration

Latex Allergy: Persons with latex allergies should not handle the FRAGMIN prefilled syringe because the needle shield may contain natural rubber latex which may cause allergic reactions.
Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep subcutaneous injection. FRAGMIN may be injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. The injection site should be varied daily. When the area around the navel or the thigh is used, using the thumb and forefinger, you **must** lift up a fold of skin while giving the injection. The entire length of the needle should be inserted at a 45 to 90-degree angle.

Inspect FRAGMIN prefilled syringes and vials visually for particulate matter and discoloration prior to administration

2.6 Pediatric Patients

FRAGMIN is not indicated for Pediatric Patients.

3 DOSAGE FORMS AND STRENGTHS

2500 IU (anti-Xa)/ 0.2 mL syringe

25000 IU (anti-Xa)/ mL syringe

10000 IU (anti-Xa)/ mL ampoule

2500 IU (anti-Xa)/ mL ampoule

4 CONTRAINDICATIONS

FRAGMIN is contraindicated in:

- Patients with active major bleeding.
- Patients with a history of heparin induced thrombocytopenia or heparin induced thrombocytopenia with thrombosis.
- Patients with prior hypersensitivity to dalteparin sodium (e.g., pruritis, rash, anaphylactic reactions) *[see Adverse Reactions (6.1)]*.
- Patients undergoing Epidural/Neuraxial anesthesia, do not administer FRAGMIN *[see Boxed Warning and Warnings and Precautions (5.1)]*;
    - As a treatment for unstable angina and non-Q-wave MI.
    - For prolonged VTE prophylaxis.
- Patients with prior hypersensitivity to heparin or pork products.

5 WARNINGS AND PRECAUTIONS

5.1Risk of Hemorrhage including Spinal/Epidural Hematomas

Spinal or epidural hemorrhage and subsequent hematomas can occur with the associated use of low molecular weight heparins or heparinoids and neuraxial (spinal/epidural) anesthesia or spinal puncture. The risk of these events is higher with the use of post-operative indwelling epidural catheters, with the concomitant use of additional drugs affecting hemostasis such as NSAIDs, with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity [*see Boxed Warning* and *Adverse Reactions (6.2) and Drug Interactions (7)*].

To reduce the potential risk of bleeding associated with the concurrent use of FRAGMIN and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of FRAGMIN [*see Clinical Pharmacology (12.3)*].

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of FRAGMIN is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. No additional hemostasis-altering medications should be administered due to the additive effects.

Patients on preoperative FRAGMIN thromboprophylaxis can be assumed to have altered coagulation. The first postoperative FRAGMIN thromboprophylaxis dose (2,500 IU) should be administered 6 to 8 hours postoperatively. The second postoperative dose (2,500 or 5,000 IU) should occur no sooner than 24 hours after the first dose. Placement or removal of a catheter should be delayed for at least 12 hours after administration of 2,500 IU once daily of FRAGMIN, at least 15 hours after the administration of 5,000 IU once daily of FRAGMIN, and at least 24 hours after the administration of higher doses (200 IU/kg once daily, 120 IU/kg twice daily) of FRAGMIN. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial hematoma will be avoided.

Although a specific recommendation for timing of a subsequent FRAGMIN dose after catheter removal cannot be made, consider delaying this next dose for at least 4 hours, based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine clearance <30mL/minute, additional considerations are necessary because elimination of FRAGMIN may be more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of FRAGMIN (2,500 IU or 5,000 IU once daily) and at least 48 hours for the higher dose (200 IU/kg once daily, 120 IU/kg twice daily) [*see Clinical Pharmacology (12.3)*].

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to report immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

Use FRAGMIN with extreme caution in patients who have an increased risk of hemorrhage, such as those with severe uncontrolled hypertension, bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal or ophthalmological surgery. FRAGMIN may enhance the risk of bleeding in patients with thrombocytopenia or platelet defects; severe liver or kidney insufficiency, hypertensive or diabetic retinopathy, and recent gastrointestinal bleeding. Bleeding can occur at any site during therapy with FRAGMIN.

5.2Thrombocytopenia

Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. The incidence of this complication is unknown at present. In clinical practice, cases of thrombocytopenia with thrombosis, amputation and death have been observed [*see Contraindications (4)*]. Closely monitor thrombocytopenia of any degree.

In FRAGMIN clinical trials supporting non-cancer indications, platelet counts of < 50,000/mm^3 occurred in < 1% of patients.

In the clinical trial of adult patients with cancer and acute symptomatic VTE treated for up to 6 months in the FRAGMIN treatment arm, platelet counts of < 100,000/mm^3 occurred in 13.6% of patients, including 6.5% who also had platelet counts less than 50,000/mm^3. In the same clinical trial, thrombocytopenia was reported as an adverse event in

10.9% of patients in the FRAGMIN arm and 8.1% of patients in the Oral Anti-Coagulant (OAC) arm. FRAGMIN dose was decreased or interrupted in patients whose platelet counts fell below 100,000/mm^3.

5.4 Laboratory Tests

Periodic routine complete blood counts, including platelet count, blood chemistry, and stool occult blood tests are recommended during the course of treatment with FRAGMIN. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are relatively insensitive measures of FRAGMIN activity and, therefore, unsuitable for monitoring the anticoagulant effect of FRAGMIN. Anti-Xa may be used to monitor the anticoagulant effect of FRAGMIN, such as in patients with severe renal impairment or if abnormal coagulation parameters or bleeding occurs during FRAGMIN therapy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in more detail in other sections of the prescribing information**.**

- Risk of Hemorrhage including Spinal/Epidural Hematomas *[see Warnings and Precautions (5.1)]*
- Thrombocytopenia *[see Warnings and Precautions (5.2)]*

6.1Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not accurately reflect the rates observed in practice.

Hemorrhage

The most commonly reported adverse reactions are hematoma at the injection site and hemorrhagic complications. The risk for bleeding varies with the indication and may increase with higher doses.

Unstable Angina and Non-Q-Wave Myocardial Infarction

Table 3 summarizes major bleeding reactions that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

Table 3

Major Bleeding Reactions in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen		
Unstable Angina and Non-Q-Wave MI	FRAGMIN 120 IU/kg/12 hr subcutaneous[1] n (%)	Heparin[2] intravenous and subcutaneous[2] n (%)	Placebo every 12 hr subcutaneous n (%)
Major Bleeding Reactions[3,4]	15/1497 (1.0)	7/731 (1.0)	4/760 (0.5)

[1] Treatment was administered for 5 to 8 days.

[2] Heparin intravenous infusion for at least 48 hours, APTT 1.5 to 2 times control, then 12,500 U subcutaneously every 12 hours for 5 to 8 days.

[3] Aspirin (75 to 165 mg per day) and beta blocker therapies were administered concurrently.

[4] Bleeding reactions were considered major if: 1) accompanied by a decrease in hemoglobin of ≥2 g/dL in connection with clinical symptoms; 2) a transfusion was required; 3) bleeding led to interruption of treatment or death; or 4) intracranial bleeding.

Hip Replacement Surgery

Table 4 summarizes: 1) all major bleeding reactions and, 2) other bleeding reactions possibly or probably related to treatment with FRAGMIN (preoperative dosing regimen), warfarin sodium, or heparin in two hip replacement surgery clinical trials.

Table 4				
Bleeding Reactions Following Hip Replacement Surgery				
Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	FRAGMIN[2] 5,000 IU once daily subcutaneous n (%)	Warfarin Sodium[1] oral n (%)	FRAGMIN[4] 5,000 IU once daily subcutaneous n (%)	Heparin 5,000 U three times a day subcutaneous n (%)
Major Bleeding Reactions[3]	7/274 (2.6)	1/279 (0.4)	0	3/69 (4.3)
Other Bleeding Reactions[5] Hematuria	8/274 (2.9)	5/279 (1.8)	0	0
Wound Hematoma	6/274 (2.2)	0	0	0
Injection Site Hematoma	3/274 (1.1)	NA	2/69 (2.9)	7/69 (10.1)

[1] Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
[2] Includes three treated patients who did not undergo a surgical procedure.
[3] A bleeding event was considered major if: 1) hemorrhage caused a significant clinical event, 2) it was associated with a hemoglobin decrease of ≥2 g/dL or transfusion of 2 or more units of blood products, 3) it resulted in reoperation due to bleeding, or 4) it involved retroperitoneal or intracranial hemorrhage.
[4] Includes two treated patients who did not undergo a surgical procedure.
[5] Occurred at a rate of at least 2% in the group treated with FRAGMIN 5,000 IU once daily.

Six of the patients treated with FRAGMIN experienced seven major bleeding reactions. Two of the reactions were wound hematoma (one requiring reoperation), three were bleeding from the operative site, one was intraoperative bleeding due to vessel damage, and one was gastrointestinal bleeding.

In the third hip replacement surgery clinical trial, the incidence of major bleeding reactions was similar in all three treatment groups: 3.6% (18/496) for patients who started FRAGMIN before surgery; 2.5% (12/487) for patients who started FRAGMIN after surgery; and 3.1% (15/489) for patients treated with warfarin sodium.

Abdominal Surgery

Table 5 summarizes bleeding reactions that occurred in clinical trials which studied FRAGMIN 2,500 and 5,000 IU administered once daily to abdominal surgery patients.

Table 5				
Bleeding Reactions Following Abdominal Surgery				
Indication	FRAGMIN vs Placebo		FRAGMIN vs FRAGMIN	
	Dosing Regimen		Dosing Regimen	
Abdominal Surgery	FRAGMIN 2,500 IU once daily subcutaneous n (%)	Placebo once daily subcutaneous n (%)	FRAGMIN 2,500 IU once daily subcutaneous n (%)	FRAGMIN 5,000 IU once daily subcutaneous n (%)

Postoperative Transfusions	14/182 (7.7)	13/182 (7.1)	89/1,025 (8.7)	125/1,033 (12.1)
Wound Hematoma	2/79 (2.5)	2/77 (2.6)	1/1,030 (0.1)	4/1,039 (0.4)
Reoperation Due to Bleeding	1/79 (1.3)	1/78 (1.3)	2/1,030 (0.2)	13/1,038 (1.3)
Injection Site Hematoma	8/172 (4.7)	2/174 (1.1)	36/1,026 (3.5)	57/1,035 (5.5)

Table 5 Cont.

Bleeding Reactions Following Abdominal Surgery

Indication	FRAGMIN vs Heparin Dosing Regimen			
Abdominal Surgery	FRAGMIN 2,500 IU once daily subcutaneous n (%)	Heparin 5,000 U twice daily subcutaneous n (%)	FRAGMIN 5,000 IU once daily subcutaneous n (%)	Heparin 5,000 U twice daily subcutaneous n (%)
Postoperative Transfusions	26/459 (5.7)	36/454 (7.9)	81/508 (15.9)	63/498 (12.7)
Wound Hematoma	16/467 (3.4)	18/467 (3.9)	12/508 (2.4)	6/498 (1.2)
Reoperation Due to Bleeding	2/392 (0.5)	3/392 (0.8)	4/508 (0.8)	2/498 (0.4)
Injection Site Hematoma	1/466 (0.2)	5/464 (1.1)	36/506 (7.1)	47/493 (9.5)

In a trial comparing FRAGMIN 5,000 IU once daily to FRAGMIN 2,500 IU once daily in patients undergoing surgery for malignancy, the incidence of bleeding reactions was 4.6% and 3.6%, respectively (n.s.). In a trial comparing FRAGMIN 5,000 IU once daily to heparin 5,000 U twice daily, in the malignancy subgroup the incidence of bleeding reactions was 3.2% and 2.7%, respectively for FRAGMIN and Heparin (n.s.).

Medical Patients with Severely Restricted Mobility During Acute Illness

Table 6summarizes major bleeding reactions that occurred in a clinical trial of medical patients with severely restricted mobility during acute illness.

Table 6

Bleeding Reactions in Medical Patients with Severely Restricted Mobility During Acute Illness

Indication	Dosing Regimen	
Medical Patients with Severely Restricted Mobility	FRAGMIN 5,000 IU once daily subcutaneous n (%)	Placebo once daily subcutaneous n (%)
Major Bleeding Reactions[1] at Day 14	8/1,848 (0.4)	0/1,833 (0)
Major Bleeding Reactions[1] at Day 21	9/1,848 (0.5)	3/1,833 (0.2)

[1] A bleeding event was considered major if: 1) it was accompanied by a decrease in hemoglobin of ≥2 g/dL in connection with clinical symptoms; 2) intraocular, spinal/epidural, intracranial, or retroperitoneal bleeding; 3) required transfusion of ≥ 2 units of blood products; 4) required significant medical or surgical intervention; or 5) led to death.

Three of the major bleeding reactions that occurred by Day 21 were fatal, all due to gastrointestinal hemorrhage (two patients in the group treated with FRAGMIN and one in the group receiving placebo).

Adult Patients with Cancer and Acute Symptomatic VTE

Table 7 summarizes the number of patients with bleeding reactions that occurred in the clinical trial of adult patients with cancer and acute symptomatic VTE. A bleeding event was considered major if it: 1) was accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical symptoms; 2) occurred at a critical site (intraocular, spinal/epidural, intracranial, retroperitoneal, or pericardial bleeding); 3) required transfusion of ≥ 2 units of blood products; or 4) led to death. Minor bleeding was classified as clinically overt bleeding that did not meet criteria for major bleeding.

At the end of the six-month study, a total of 46 (13.6%) patients in the FRAGMIN arm and 62 (18.5%) patients in the OAC arm experienced any bleeding event. One bleeding event (hemoptysis in a patient in the FRAGMIN arm at Day 71) was fatal.

Table 7

Bleeding Reactions (Major and Any) (As treated population)[1]

Study period	FRAGMIN 200 IU/kg (max. 18,000 IU) subcutaneous once daily x 1 month, then 150 IU/kg (max. 18,000 IU) subcutaneous once daily x 5 months			OAC FRAGMIN 200 IU/kg (max 18,000 IU) subcutaneous once daily x 5-7 days and OAC for 6 months (target INR 2-3)		
	Number at risk	Patients with Major Bleeding n (%)	Patients with Any Bleeding n (%)	Number at risk	Patients with Major Bleeding n (%)	Patients with Any Bleeding n (%)
Total during study	338	19 (5.6)	46 (13.6)	335	12 (3.6)	62 (18.5)
Week 1	338	4 (1.2)	15 (4.4)	335	4 (1.2)	12 (3.6)
Weeks 2-4	332	9 (2.7)	17 (5.1)	321	1 (0.3)	12 (3.7)
Weeks 5-28	297	9 (3.0)	26 (8.8)	267	8 (3.0)	40 (15.0)

[1] Patients with multiple bleeding episodes within any time interval were counted only once in that interval. However, patients with multiple bleeding episodes that occurred at different time intervals were counted once in each interval in which the event occurred.

Elevations of Serum Transaminases

In FRAGMIN clinical trials supporting non-cancer indications, where hepatic transaminases were measured, asymptomatic increases in transaminase levels (SGOT/AST and SGPT/ALT) greater than three times the upper limit of normal of the laboratory reference range were seen in 4.7% and 4.2%, respectively, of patients during treatment with FRAGMIN.

In the FRAGMIN clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated with FRAGMIN for up to 6 months, asymptomatic increases in transaminase levels, AST and ALT, greater than three times the upper limit of normal of the laboratory reference range were reported in 8.9% and 9.5% of patients, respectively. The frequencies of Grades 3 and 4 increases in AST and ALT, as classified by the National Cancer Institute, Common Toxicity Criteria (NCI-CTC) Scoring System, were 3% and 3.8%, respectively. Grades 2, 3 & 4 combined have been reported in 12% and 14% of patients, respectively.

Other

Allergic Reactions: Allergic reactions (i.e., pruritus, rash, fever, injection site reaction, bullous eruption) have occurred. Cases of anaphylactoid reactions have been reported.

***Local Reactions**:* Pain at the injection site was reported in 4.5% of patients treated with FRAGMIN 5,000 IU once daily vs 11.8% of patients treated with heparin 5,000 U twice daily in the abdominal surgery trials. In the hip replacement trials, pain at injection site was reported in 12% of patients treated with FRAGMIN 5,000 IU once daily vs 13% of patients treated with heparin 5,000 U three times a day.

6.2 Post Marketing Experience

The following adverse reactions have been identified during postapproval use of FRAGMIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Since first international market introduction in 1985, there have been more than 15 reports of epidural or spinal hematoma formation with concurrent use of FRAGMIN and spinal/epidural anesthesia or spinal puncture. The majority of patients had postoperative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. In some cases the hematoma resulted in long-term or permanent paralysis (partial or complete) [*see Boxed Warning*].

Musculoskeletal System: Osteoporosis

Skin or subcutaneous tissues disorders: Skin necrosis, cases of alopecia reported that improved on drug discontinuation

6.3 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

7 DRUG INTERACTIONS

The use of FRAGMIN in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents may increase the increased risk of bleeding [*see Warnings and Precautions (5)*].

8 USE IN SPECIFIC POPULATIONS

8.1Pregnancy

Risk Summary

Available data from published literature and postmarketing reports have not reported a clear association with FRAGMIN and adverse developmental outcomes. There are risks to the mother associated with untreated VTE in pregnancy, and a potential for adverse effects on the preterm infant when FRAGMIN is used in pregnancy *(see Clinical Considerations)*. In animal reproduction studies, there was no evidence of embryo-fetal toxicity or teratogenicity when dalteparin sodium was administered to pregnant rats and rabbits during organogenesis at doses 2 to 4 times (rats) and 4 times (rabbits) the human dose of 100 IU/kg dalteparin based on the body surface area *(see Data)*. Because animal reproduction studies are not always predictive of human response, FRAGMIN should be used during pregnancy only if clearly needed.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data describe that women with a previous history of VTE in pregnancy are at higher risk for recurrence during subsequent pregnancies compared to those with no risk factor for VTE (4.5% versus 2.7% respectively, relative risk 1.7, 95% CI: 1.0-2.8).

Data

Animal Data

In reproductive and developmental toxicity studies, pregnant rats and rabbits received dalteparin sodium during organogenesis at intravenous doses up to 2,400 IU/kg (14,160 IU/m^2) (rats) and 4,800 IU/kg (40,800 IU/m^2) (rabbits). These exposures were 2 to 4 times (rats) and 4 times (rabbits) the human dose of 100 IU/kg dalteparin based on the body surface area. These studies revealed no evidence of teratogenicity or embryo-fetal toxicity.

8.2 Lactation

Risk Summary

Limited published data indicate that dalteparin is present in human milk in small amounts *(see Data)*. No adverse effects on the breastfed infant have been reported. There are no data on the effects of the drug on milk production. Oral absorption of dalteparin is expected to be low, but the clinical implications, if any, of this small amount of anticoagulant activity on a breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FRAGMIN and any potential adverse effects on the breastfed child from FRAGMIN or from the underlying maternal condition.

Data

A study evaluated samples of maternal blood and breast milk in 15 lactating women receiving prophylactic doses of dalteparin in the immediate postpartum period (days 4-8 after Cesarean-section). The samples were collected before and 3-4 hours after daily injections of 2500 IU dalteparin. Small amounts of anti-Xa activity (range<0.005 to 0.037 IU/mL) in breast milk were detected in 11 of the 15 women. Because this study evaluated colostrum or transitional milk at a single timepoint during the 24-hour dosing interval, the clinical relevance of this data is unclear in regard to passage of drug into mature milk and the quantification of drug exposure to the infant over the full dosing interval.

8.3 Geriatric Use

Of the total number of patients in clinical studies of FRAGMIN, 5,516 patients were 65 years of age or older and 2,237 were 75 or older. No overall differences in effectiveness were observed between these subjects and younger subjects. Some studies suggest that the risk of bleeding increases with age. Postmarketing surveillance and literature reports have not revealed additional differences in the safety of FRAGMIN between elderly and younger patients. Give careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) in geriatric patients, particularly in those with low body weight (< 45 kg) and those predisposed to decreased renal function [*see Warnings and Precautions (5) and Clinical Pharmacology (12)*].

10 OVERDOSAGE

An excessive dosage of FRAGMIN Injection may lead to hemorrhagic complications. These may generally be stopped by slow intravenous injection of protamine sulfate (1% solution), at a dose of 1 mg protamine for every 100 anti-Xa IU of FRAGMIN given. If the APTT measured 2 to 4 hours after the first infusion remains prolonged, a second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of FRAGMIN may be administered. Even with these additional doses of protamine, the APTT may remain more prolonged than would usually be found following administration of unfractionated heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60 to 75%).

Take particular care to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, give protamine sulfate only when resuscitation techniques and treatment for anaphylactic shock are readily available. For additional information, consult the labeling of Protamine Sulfate Injection, USP, products.

11 DESCRIPTION

FRAGMIN (dalteparin sodium solution for injection) is a sterile, low molecular weight heparin.

It is available in prefilled syringes and ampoules [*see how supplied/storage and handling (16*)].

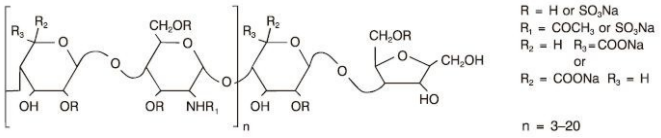
List of excipients:
Sodium Chloride, Sodium hydroxide or hydrochloride acid (for pH adjustment), Water for Injections.

The prefilled syringes and ampules are preservative-free.

Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulfated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5,000 and about 90% of the material within the range 2,000–9,000. The molecular weight distribution is:

<	3000 daltons	3.0–15%
	3,000 to 8,000 daltons	65.0–78.0%
>	8,000 daltons	14.0–26.0%

STRUCTURAL FORMULA



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dalteparin is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In humans, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting the activated partial thromboplastin time (APTT).

12.2 Pharmacodynamics

Doses of FRAGMIN Injection of up to 10,000 anti-Factor Xa IU administered subcutaneously as a single dose or two 5,000 IU doses 12 hours apart to healthy subjects did not produce a significant change in platelet aggregation, fibrinolysis, or global clotting tests such as prothrombin time (PT), thrombin time (TT) or APTT. Subcutaneous administration of doses of 5,000 IU twice daily of FRAGMIN for seven consecutive days to patients undergoing abdominal surgery did not markedly affect APTT, Platelet Factor 4 (PF4), or lipoprotein lipase.

12.3 Pharmacokinetics

Adults

Mean peak levels of plasma anti-Xa activity following single subcutaneous doses of 2,500, 5,000 and 10,000 IU were 0.19 ± 0.04, 0.41 ± 0.07 and 0.82 ± 0.10 IU/mL, respectively, and were attained in about 4 hours in most subjects. Absolute bioavailability in healthy volunteers, measured as the anti-Xa activity, was 87 ± 6%. Increasing the dose from 2,500 to 10,000 IU resulted in an overall increase in anti-Xa AUC that was greater than proportional by about one-third.

Peak anti-Xa activity increased more or less linearly with dose over the same dose range. There appeared to be no appreciable accumulation of anti-Xa activity with twice-daily dosing of 100 IU/kg subcutaneously for up to 7 days.

The volume of distribution for dalteparin anti-Xa activity was 40 to 60 mL/kg. The mean plasma clearances of dalteparin anti-Xa activity in normal volunteers following single intravenous bolus doses of 30 and 120 anti-Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 mL/hr/kg, respectively. The corresponding mean disposition half-lives were 1.47 ± 0.3 and 2.5 ± 0.3 hours.

Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer apparent terminal half-lives (3 to 5 hours) are observed following subcutaneous dosing, possibly due to delayed absorption. In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Xa activity following a single intravenous dose of 5,000 IU FRAGMIN 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dalteparin sodium has not been tested for its carcinogenic potential in long-term animal studies. It was not mutagenic in the ***in vitro*** Ames Test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and in the ***in vivo*** mouse micronucleus test. Dalteparin sodium at subcutaneous doses up to 1,200 IU/kg (7,080 IU/m^2) did not affect the fertility or reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction

In a double-blind, randomized, placebo-controlled clinical trial, patients who recently experienced unstable angina with EKG changes or non-Q-wave myocardial infarction (MI) were randomized to FRAGMIN Injection 120 IU/kg or placebo every 12 hours subcutaneously. In this trial, unstable angina was defined to include only angina with EKG changes. All patients, except when contraindicated, were treated concurrently with aspirin (75 mg once daily) and beta blockers. Treatment was initiated within 72 hours of the event (the majority of patients received treatment within 24 hours) and continued for 5 to 8 days. A total of 1,506 patients were enrolled and treated; 746 received FRAGMIN and 760 received placebo. The mean age of the study population was 68 years (range 40 to 90 years) and the majority of patients were white (99.7%) and male (63.9%). The combined incidence of the endpoint of death or myocardial infarction was lower for FRAGMIN compared with placebo at 6 days after initiation of therapy. These results were observed in an analysis of all-randomized and all-treated patients. The combined incidence of death, MI, need for intravenous heparin or intravenous. nitroglycerin, and revascularization was also lower for FRAGMIN than for placebo (see Table 8).

Table8

Efficacy of FRAGMIN in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen	
	FRAGMIN 120 IU/kg/every 12 hr subcutaneous n (%)	Placebo every 12 hr subcutaneous n (%)
All Treated Unstable Angina and Non-Q-Wave MI Patients	746	760
Primary Endpoints - 6 day timepoint Death, MI	13/741 (1.8)[1]	36/757 (4.8)

Table8		
Efficacy of FRAGMIN in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction		
Indication	Dosing Regimen	
	FRAGMIN 120 IU/kg/every 12 hr subcutaneous n (%)	Placebo every 12 hr subcutaneous n (%)
Secondary Endpoints - 6 day timepoint Death, MI, intravenous heparin, i.v. nitroglycerin, Revascularization	59/739 (8.0)[1]	106/756 (14.0)

[1] p-value = 0.001

In a second randomized, controlled trial designed to evaluate long-term treatment with FRAGMIN (days 6 to 45), data were also collected comparing 1-week (5 to 8 days) treatment of FRAGMIN 120 IU/kg every 12 hours subcutaneously with heparin at an APTT-adjusted dosage. All patients, except when contraindicated, were treated concurrently with aspirin (100 to 165 mg per day). Of the 1,499 patients enrolled, 1,482 patients were treated; 751 received FRAGMIN and 731 received heparin. The mean age of the study population was 64 years (range 25 to 92 years) and the majority of patients were white (96.0%) and male (64.2%). The incidence of the combined endpoint of death, myocardial infarction, or recurrent angina during this 1-week treatment period (5 to 8 days) was 9.3% for FRAGMIN and 7.6% for heparin (p=0.323).

14.2 Prophylaxis of Deep Vein Thrombosis in Patients Following Hip Replacement Surgery

In an open-label randomized study, FRAGMIN 5,000 IU administered once daily subcutaneously was compared with warfarin sodium, administered orally, in patients undergoing hip replacement surgery. Treatment with FRAGMIN was initiated with a 2,500 IU dose subcutaneously within 2 hours before surgery, followed by a 2,500 IU dose subcutaneously the evening of the day of surgery. Then, a dosing regimen of FRAGMIN 5,000 IU subcutaneously once daily was initiated on the first postoperative day. The first dose of warfarin sodium was given the evening before surgery, then continued daily at a dose adjusted for INR 2 to 3. Treatment in both groups was then continued for 5 to 9 days postoperatively. Of the 580 patients enrolled, 553 were treated and 550 underwent surgery. Of those who underwent surgery, 271 received FRAGMIN and 279 received warfarin sodium. The mean age of the study population was 63 years (range 20 to 92 years) and the majority of patients were white (91.1%) and female (52.9%). The incidence of deep vein thrombosis (DVT), as determined by evaluable venography, was significantly lower for the group treated with FRAGMIN compared with patients treated with warfarin sodium (see Table9).

Table 9		
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery		
Indication	Dosing Regimen	
	FRAGMIN 5,000 IU once daily[1] subcutaneous n (%)	Warfarin Sodium once daily[2] oral n (%)
All Treated Hip Replacement Surgery Patients	271	279
Treatment Failures in Evaluable Patients DVT, Total	28/192 (14.6)[3]	49/190 (25.8)
Proximal DVT	10/192 (5.2)[4]	16/190 (8.4)
PE	2/271 (0.7)	2/279 (0.7)

[1] The daily dose on the day of surgery was divided: 2,500 IU was given 2 hours before surgery and again in the evening of the day of surgery.

[2] Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5
[3] p-value = 0.006
[4] p-value = 0.185

In a second single-center, double-blind study of patients undergoing hip replacement surgery, FRAGMIN 5,000 IU once daily subcutaneously starting the evening before surgery, was compared with heparin 5,000 U subcutaneously three times a day, starting the morning of surgery. Treatment in both groups was continued for up to 9 days postoperatively. Of the 140 patients enrolled, 139 were treated and 136 underwent surgery. Of those who underwent surgery, 67 received FRAGMIN and 69 received heparin. The mean age of the study population was 69 years (range 42 to 87 years) and the majority of patients were female (58.8%). In the intent-to-treat analysis, the incidence of proximal DVT was significantly lower for patients treated with FRAGMIN compared with patients treated with heparin (6/67 vs 18/69; p=0.012). The incidence of pulmonary embolism detected by lung scan was also significantly lower in the group treated with FRAGMIN (9/67 vs 19/69; p=0.032).

A third multi-center, double-blind, randomized study evaluated a postoperative dosing regimen of FRAGMIN for thromboprophylaxis following total hip replacement surgery. Patients received either FRAGMIN or warfarin sodium, randomized into one of three treatment groups. One group of patients received the first dose of FRAGMIN 2,500 IU subcutaneous within 2 hours before surgery, followed by another dose of FRAGMIN 2,500 IU subcutaneous at least 4 hours (6.6 ± 2.3 hr) after surgery. Another group received the first dose of FRAGMIN 2,500 IU subcutaneous at least 4 hours (6.6 ± 2.4 hr) after surgery. Then, **both** of these groups began a dosing regimen of FRAGMIN 5,000 IU once daily subcutaneous on postoperative day 1. The third group of patients received warfarin sodium the evening of the day of surgery, then continued daily at a dose adjusted to maintain INR 2 to 3. Treatment for all groups was continued for 4 to 8 days postoperatively, after which time all patients underwent bilateral venography.

In the total enrolled study population of 1,501 patients, 1,472 patients were treated; 496 received FRAGMIN (first dose before surgery), 487 received FRAGMIN (first dose after surgery) and 489 received warfarin sodium. The mean age of the study population was 63 years (range 18 to 91 years) and the majority of patients were white (94.4%) and female (51.8%).

Administration of the first dose of FRAGMIN after surgery was as effective in reducing the incidence of thromboembolic reactions as administration of the first dose of FRAGMIN before surgery (44/336 vs 37/338; p=0.448). Both dosing regimens of FRAGMIN were more effective than warfarin sodium in reducing the incidence of thromboembolic reactions following hip replacement surgery.

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

Abdominal surgery patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes, or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism.

FRAGMIN administered once daily subcutaneously beginning prior to surgery and continued for 5 to 10 days after surgery, reduced the risk of DVT in patients at risk for thromboembolic complications in two double-blind, randomized, controlled clinical trials performed in patients undergoing major abdominal surgery. In the first study, a total of 204 patients were enrolled and treated; 102 received FRAGMIN and 102 received placebo. The mean age of the study population was 64 years (range 40 to 98 years) and the majority of patients were female (54.9%). In the second study, a total of 391 patients were enrolled and treated; 195 received FRAGMIN and 196 received heparin. The mean age of the study population was 59 years (range 30 to 88 years) and the majority of patients were female (51.9%). FRAGMIN 2,500 IU was superior to placebo and similar to heparin in reducing the risk of DVT (see Tables 10 and 11).

Table 10		
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery		
Indication	Dosing Regimen	
	FRAGMIN 2,500 IU once daily subcutaneous n (%)	Placebo once daily subcutaneous n (%)
All Treated Abdominal Surgery Patients	102	102
Treatment Failures in Evaluable Patients Total Thromboembolic Reactions	4/91 (4.4)[1]	16/91 (17.6)
Proximal DVT	0	5/91 (5.5)
Distal DVT	4/91 (4.4)	11/91 (12.1)
PE	0	2/91 (2.2)[2]

[1] p-value = 0.008
[2] Both patients also had DVT, 1 proximal and 1 distal

Table 11		
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery		
Indication	Dosing Regimen	
	FRAGMIN 2,500 IU once daily subcutaneous n (%)	Heparin 5,000 U twice daily subcutaneous n (%)
All Treated Abdominal Surgery Patients	195	196
Treatment Failures in Evaluable Patients Total Thromboembolic Reactions	7/178 (3.9)[1]	7/174 (4.0)
Proximal DVT	3/178 (1.7)	4/174 (2.3)
Distal DVT	3/178 (1.7)	3/174 (1.7)
PE	1/178 (0.6)	0

[1] p-value = 0.74

In a third double-blind, randomized study performed in patients undergoing major abdominal surgery with malignancy, FRAGMIN 5,000 IU subcutaneous once daily was compared with FRAGMIN 2,500 IU subcutaneous once daily. Treatment was continued for 6 to 8 days. A total of 1,375 patients were enrolled and treated; 679 received FRAGMIN 5,000 IU and 696 received 2,500 IU. The mean age of the combined groups was 71 years (range 40 to 95 years). The majority of patients were female (51.0%). FRAGMIN 5,000 IU once daily was more effective than FRAGMIN 2,500 IU once daily in reducing the risk of DVT in patients undergoing abdominal surgery with malignancy (see Table12).

Table 12		
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery		
Indication	Dosing Regimen	
	FRAGMIN 2,500 IU once daily subcutaneous n (%)	FRAGMIN 5,000 IU once daily subcutaneous n (%)
All Treated Abdominal Surgery	696	679

Table 12 Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery		
Indication	Dosing Regimen	
	FRAGMIN 2,500 IU once daily subcutaneous n (%)	FRAGMIN 5,000 IU once daily subcutaneous n (%)
Patients[1]		
Treatment Failures in Evaluable Patients Total Thromboembolic Reactions	99/656 (15.1)[2]	60/645 (9.3)
Proximal DVT	18/657 (2.7)	14/646 (2.2)
Distal DVT	80/657 (12.2)	41/646 (6.3)
PE		
Fatal	1/674 (0.1)	1/669 (0.1)
Non-fatal	2	4

[1] Major abdominal surgery with malignancy
[2] p-value = 0.001

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

In a double-blind, multi-center, randomized, placebo-controlled clinical trial, general medical patients with severely restricted mobility who were at risk of VTE were randomized to receive either FRAGMIN 5,000 IU or placebo subcutaneously once daily during Days 1 to 14 of the study. These patients had an acute medical condition requiring a projected hospital stay of at least 4 days, and were confined to bed during waking hours. The study included patients with congestive heart failure (NYHA Class III or IV), acute respiratory failure not requiring ventilatory support, and the following acute conditions with at least one risk factor occurring in > 1% of treated patients: acute infection (excluding septic shock), acute rheumatic disorder, acute lumbar or sciatic pain, vertebral compression, or acute arthritis of the lower extremities. Risk factors include > 75 years of age, cancer, previous DVT/PE, obesity and chronic venous insufficiency. A total of 3,681 patients were enrolled and treated: 1,848 received FRAGMIN and 1,833 received placebo. The mean age of the study population was 69 years (range 26 to 99 years), 92.1% were white and 51.9% were female. The primary efficacy endpoint was evaluated at Day 21 and was defined as at least one of the following within Days 1 to 21 of the study: asymptomatic DVT (diagnosed by compression ultrasound), a confirmed symptomatic DVT, a confirmed pulmonary embolism or sudden death. The follow-up extended through Day 90.

When given at a dose of 5,000 IU once a day subcutaneously, FRAGMIN significantly reduced the incidence of thromboembolic reactions including verified DVT by Day 21 (see Table13). The prophylactic effect was sustained through Day 90.

Table 13		
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility During Acute Illness		
Indication	Dosing Regimen	
	FRAGMIN 5,000 IU once daily subcutaneous n (%)	Placebo once daily subcutaneous n (%)
All Treated Medical Patients During Acute Illness	1,848	1,833
Treatment failure in evaluable patients (Day 21)[1] DVT, PE, or sudden death	42/1,518 (2.8)[2]	73/1,473 (5.0)
Total Thromboembolic Reactions (Day 21)	37/1,513 (2.5)	70/1,470 (4.8)
Total DVT	32/1,508 (2.1)	64/1,464 (4.4)
Proximal DVT	29/1,518 (1.9)	60/1,474 (4.1)
Symptomatic VTE	10/1,759 (0.6)	17/1,740 (1.0)
PE	5/1,759 (0.3)	6/1,740 (0.3)
Sudden Death	5/1,829 (0.3)	3/1,807 (0.2)

[1] Defined as DVT (diagnosed by compression ultrasound at Day 21 + 3), confirmed symptomatic DVT, confirmed PE or sudden death.
[2] p-value = 0.0015

14.5 Patients with Cancer and Acute Symptomatic VTE

Adult PatientsIn a prospective, multi-center, open-label, clinical trial, 676 patients with cancer and newly diagnosed, objectively confirmed acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were studied. Patients were randomized to either FRAGMIN 200 IU/kg subcutaneous (max 18,000 IU subcutaneous daily for one month) then 150 IU/kg subcutaneous (max 18,000 IU subcutaneous daily for five months (FRAGMIN arm) or FRAGMIN 200 IU/kg subcutaneous (max 18,000 IU subcutaneous daily for five to seven days and oral anticoagulant for six months (OAC arm). In the OAC arm, oral anticoagulation was adjusted to maintain an INR of 2 to 3. Patients were evaluated for recurrence of symptomatic VTE every two weeks for six months.

The median age of patients was 64 years (range: 22 to 89 years); 51.5% of patients were females; 95.3% of patients were Caucasians. Types of tumors were: gastrointestinal tract (23.7%), genito-urinary (21.5%), breast (16%), lung (13.3%), hematological tumors (10.4%), and other tumors (15.1%).

A total of 27 (8.0%) and 53 (15.7%) patients in the FRAGMIN and OAC arms, respectively, experienced at least one episode of an objectively confirmed, symptomatic DVT and/or PE during the 6-month study period. Most of the difference occurred during the first month of treatment (see Table 14). The benefit was maintained over the 6-month study period.

Table 14						
Recurrent VTE in Patients with Cancer (Intention to treat population)[1]						
Study Period	FRAGMIN arm			OAC arm		
	FRAGMIN 200 IU/kg (max. 18,000 IU) subcutaneous once daily x 1 month, then 150 IU/kg (max. 18,000 IU) subcutaneous once daily x 5 months			FRAGMIN 200 IU/kg (max 18,000 IU) subcutaneous once daily x 5-7 days and OAC for 6 months (target INR 2-3)		
	Number at Risk	Patients with VTE	%	Number at Risk	Patients with VTE	%
Total	338	27	8.0	338	53	15.7

Week 1	338	5	1.5	338	8	2.4
Weeks 2-4	331	6	1.8	327	25	7.6
Weeks 5-28	307	16	5.2	284	20	7.0

[1] Three patients in the FRAGMIN arm and 5 patients in the OAC arm experienced more than 1 VTE over the 6-month study period.

In the intent-to-treat population that included all randomized patients, the primary comparison of the cumulative probability of the first VTE recurrence over the 6-month study period was statistically significant ($p < 0.01$) in favor of the FRAGMIN arm, with most of the treatment difference evident in the first month.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dosage Form	Strength	Package Size
Prefilled Syringe	2500 IU (anti-Xa)/ 0.2 mL	10×0.2 mL
	25000 IU (anti-Xa)/ mL	0.2 mL
		0.3 mL
		0.4 mL
		0.5 mL
		0.6 mL
		0.72 mL
Ampoule	10000 IU (anti-Xa)/ mL	10×1 mL
Ampoule	2500 IU (anti-Xa)/ mL	10×4 mL

Storage
Store below 25°C.

Shelf life
The expiry date of the product is indicated on the packaging materials.

Latex Allergy: The needle shield of the prefilled syringe may contain natural rubber latex *[see Administration (2.5)]*.

17 MANUFACTURER

Pfizer Manufacturing Belgium NV, Puurs, Belgium.

18 LICENCE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St. Herzliya Pituach 46725.

19 LICENSE NUMBERS

FRAGMIN® 2500 IU /0.2 ML 123-11-26544
FRAGMIN® 2500 IU/ML 125-12-26545
FRAGMIN® 10000 IU/ML 123-12-26547
FRAGMIN® 25000 IU/ML 053-52-26546

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