פייזר פי אף אי פרמצבטיקה ישראל בע"מ
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הרצליה פיתוח, ישראל 46725
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אוקטובר 2020

רופא/ה, רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלון לרופא של התכשירים:

Fragmin® 2500 IU /0.2 ML; Fragmin® 2500 IU/ML; Fragmin® 10000 IU/ML; Fragmin® 25000 IU/ML

הרכב וחוזק:
Dalteparin Sodium; 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; 18,000 IU (anti-Factor Xa)/ 0.72 mL; 2,500 IU (anti- Factor Xa)/ ml; 10,000 IU (anti- Factor Xa)/ ml

התוויה:
- 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.

להלן העדכונים העיקריים בעלון לרופא:

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

2 DOSAGE AND ADMINISTRATION

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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

4 CONTRAINDICATIONS

FRAGMIN is contraindicated in:

- Patients with a history of heparin induced thrombocytopenia or heparin induced thrombocytopenia with thrombosis.
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5 WARNINGS AND PRECAUTIONS

5.1 Risk 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.

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.

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).

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.

5.2 Thrombocytopenia

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. 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.

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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. …

6 ADVERSE REACTIONS

6.1 Clinical 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.

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Other

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

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6.2 Post Marketing Experience

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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

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8 USE IN SPECIFIC POPULATIONS

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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.

8.3Geriatric 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.

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Latex Allergy: The needle shield of the prefilled syringe may contain natural rubber latex.

השינויים המודגשים ברקע צהוב מהויים החמרה. כמו כן בוצעו שינויים נוספים הכוללים תוספת מידע ועדכוני נוסח שאינם מהווים החמרה.

העלון המעודכן נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות:
https://data.health.gov.il/drugs/index.html#!/byDrug

לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פי אף אי פרמצבטיקה ישראל בע"מ,
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בברכה,
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