Your doctor is the best resource for medical advice and information. The health information contained herein is provided for educational / awareness purposes only and is not intended to replace discussions with a medical practitioner and/or medical advice or be construed as a promotional information.

Package leaflet: information for the user
Dalteparin sodium solution for injection syringe 2,500 IU (anti-Factor Xa)/0.2 ml
Dalteparin sodium solution for injection syringe 5,000 IU (anti-Factor Xa)/0.2 ml
Dalteparin sodium solution for injection vial 10,000 IU (anti-Factor Xa)/1 ml in 10 ml
Dalteparin sodium solution for injection vial FRAGMIN®

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What FRAGMIN Solution for Injection is and what it is used for
2. What you need to know before you use FRAGMIN Solution for Injection
3. How to use FRAGMIN Solution for Injection
4. Possible side effects
5. How to store FRAGMIN Solution for Injection
6. Contents of the pack and other information

1. What FRAGMIN Solution for Injection is and what it is used for

FRAGMIN Solution for Injection belongs to the group of anticoagulants (agents which delay blood clotting). It is an antithrombotic medicine (meaning that it prevents the formation of blood clots), containing dalteparin sodium, a low molecular weight heparin.

FRAGMIN Solution for Injection is used to:
- Treat the acute formation of blood clots in deep veins.
- Prevent clotting in blood dialysis and filtration equipment in patients with acute kidney failure or chronic kidney disease.

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- Prevent blood clotting (coagulation) when surgery is performed.
- Prevent clotting in those at risk when mobility is restricted during acute illness.
- Treat unstable coronary artery disease.
- Treat symptomatic blood clots to prevent recurrence of the clots in patients with cancer.

2. What you need to know before you use FRAGMIN Solution for Injection

Do not use FRAGMIN Solution for Injection
- If, in the past, you have been diagnosed or suspected with a decreased number of platelets (cells that promote blood clotting) due to heparin in your blood, a condition called thrombocytopenia.
- If you have a stomach or intestine ulcer or bleeding.
- In cases of bleeding (haemorrhage) in the brain, or other active bleeding.
- If you have a severe blood clotting disorder.
- In cases of bacterial infection of the heart (septic endocarditis).
- If you have an injury or have had surgery on your central nervous system, eyes or ears.
- If you are allergic (hypersensitive) to dalteparin sodium, or any of the other ingredients of this medicine (listed in section 6), or to other low molecular weight heparins, or heparins, or products of pork origin.
- Epidural anaesthesia (injection into the epidural space in the vertebrae), spinal anaesthesia (injection into the intervertebral spinal fluid) and lumbar puncture (spinal tap) are contraindicated during treatment with high doses of FRAGMIN Solution for Injection, such as those necessary for the treatment of acute formation of blood clots in deep veins (acute deep vein thrombosis), obstruction of a blood vessel in the lung or unstable coronary artery disease.

Warnings and precautions
Talk to your doctor before using FRAGMIN Solution for Injection:
- If you are allergic to heparin-based preparations and/or preparations based on low molecular weight heparin.
- If you have a known or possible allergy to latex (natural rubber) or if the needle guard on FRAGMIN Solution for Injection prefilled syringes will be handled by someone with a known or possible allergy to latex (natural rubber). The needle guard of FRAGMIN Solution for Injection prefilled syringes may contain latex (natural rubber) which may cause a severe allergic reaction in people with a latex (natural rubber) allergy.
- If the number of platelets in your blood is reduced (thrombocytopenia) and/or if you have a disorder of the platelets.
- In severe hepatic impairment (significant failure of liver function).
- In severe renal impairment (significant failure of kidney function).
- If you have uncontrolled hypertension (high blood pressure).
- In case of retinal (eye) problems due to diabetes or hypertension (retinopathy).
- In case of high dose treatment with FRAGMIN Solution for Injection , in particular for the treatment of an acute formation of blood clots in deep veins (acute deep vein thrombosis), obstruction of a blood vessel in the lung or unstable coronary artery disease.
- In case of acute myocardial infarction.
- If you are to undergo a lumbar puncture or epidural or spinal anaesthesia.
- If you have artificial heart valves.
- If you have recently had surgery or need to undergo surgery in the near future.

When this medicinal product is used before spinal or epidural anaesthesia, a doctor should be notified immediately if any of these signs occur: pain in the middle back, difficulty moving, strange sensations, functional problems with the intestine and the bladder.

FRAGMIN Solution for Injection may cause an increase in potassium levels in the blood, in particular:
- If you have diabetes mellitus.
- If you have chronic renal impairment.
- In case of pre-existing high blood acidity.
- If you have a high serum potassium level.
- If you are taking potassium-sparing medicines.
- In case of prolonged treatment with FRAGMIN Solution for Injection.

This medicine requires close monitoring in:
- Children.
- Patients whose kidneys function poorly.
- Patients treated while under acute haemodialysis and haemofiltration (blood purification methods).
- Very thin or morbidly obese patients.
- Pregnant women.
- Patients with an increased risk of bleeding (haemorrhage) or recurrence of blood clots (thrombosis).
- Elderly patients.

Children
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, close monitoring is required.

FRAGMIN Solution for Injection products that contain benzyl alcohol should not be used in young children (under 3 years of age) for more than one week unless advised otherwise by the doctor (see section “FRAGMIN Solution for Injection contains benzyl alcohol and sodium”).

Other medicines and FRAGMIN Solution for Injection
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Thrombolytic (clot-dissolving) treatment or certain medicines which affect blood clotting may increase the risk of haemorrhage (bleeding) when combined with FRAGMIN Solution for Injection:
- Platelet inhibitors (used to decrease platelet aggregation and reduce the risk of blood clots).
- Thrombolytics (used to dissolve blood clots).
- Aspirin (acetylsalicylic acid).
- Nonsteroidal anti-inflammatories (NSAIDs) (medicines used to treat inflammation).
- Antagonists of GP IIb/IIIa receptors (medicines affecting platelet aggregation, used to treat cardiac disorders).
- Antagonists of vitamin K and other types of anticoagulants.
- Dextran (used in certain artificial tears).

Particular care should be taken in patients with renal impairment during simultaneous administration of FRAGMIN Solution for Injection and NSAIDs or aspirin at higher doses. In patients with unstable coronary artery disease, aspirin should be taken at low doses only.

Medicines that can reduce the effect of FRAGMIN Solution for Injection include:
- Andexanet alfa (medicine used to reverse the effects of certain blood thinning medications, such as apixaban or rivaroxaban).

Interaction between FRAGMIN Solution for Injection and the following substances cannot be excluded:
- Intravenous nitroglycerin (used to treat certain cardiac disorders).
- Penicillin (an antibiotic) at high doses.
- Sulfinpyrazone (used to treat gout among other problems).
- Probenecid (used to treat gout among other problems).
- Ethacrynic acid (a diuretic, used to treat cardiac disorders or oedema).
- Cytostatic agents (a type of medicine used in chemotherapy).
- Quinine (mainly used to treat malaria).
- Antihistamines (anti-allergic medicines).
- Digitalis (a medicine commonly used to treat heart disease).
- Tetracyclines (antibiotics).
- Tobacco.
- Ascorbic acid (vitamin C).

FRAGMIN Solution for Injection with food, drink and alcohol
Not applicable.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
The use of FRAGMIN Solution for Injection has been studied in pregnant women. No toxic effects were found in connection with the progress of pregnancy, or the health of the foetus or newborn infant.

Epidural anaesthesia during childbirth is contraindicated in women being treated with high doses of FRAGMIN Solution for Injection (see "Do not use FRAGMIN Solution for Injection "). FRAGMIN Solution for Injection should be used with caution in patients at high risk of haemorrhage (bleeding), especially in pregnant women.

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml multidose vial) contains benzyl alcohol, a preservative that crosses the placenta. It is recommended to use FRAGMIN Solution for Injection products that do not contain benzyl alcohol during pregnancy (see "FRAGMIN Solution for Injection contains benzyl alcohol and sodium").

Breast-feeding
Small amounts of FRAGMIN Solution for Injection are excreted in breast milk. Only limited information is currently available, and a risk to breast-fed infants cannot be excluded. The decision to continue or discontinue breast-feeding or to continue or discontinue therapy with FRAGMIN

Solution for Injection should be made taking into account the benefit of breast-feeding for the child and the benefit of FRAGMIN Solution for Injection treatment for the mother.

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml multidose) vial contains benzyl alcohol, a preservative that may pass into breast milk. It is recommended to use FRAGMIN Solution for Injection products that do not contain benzyl alcohol to treat women who are breast-feeding (see "FRAGMIN Solution for Injection contains benzyl alcohol and sodium").

Fertility
No effect of FRAGMIN Solution for Injection on fertility were noted when tested in animals.

Driving and using machines
FRAGMIN Solution for Injection has no effect on the ability to drive and use machines.

FRAGMIN Solution for Injection contains benzyl alcohol and sodium
FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml multidose vial) presentation contains benzyl alcohol.

There are FRAGMIN Solution for Injection products available that do not contain any benzyl alcohol.

Benzyl alcohol may cause allergic reactions. Benzyl alcohol has also been associated with the risk of serious side effects, in particular breathing problems (called "gasping syndrome") in young children. FRAGMIN Solution for Injection products that contain benzyl alcohol should not be used in young children (under 3 years of age) for more than one week unless advised otherwise by the doctor. Taking large quantities of these FRAGMIN Solution for Injection products may lead to the accumulation of benzyl alcohol in your body, resulting in an increase of the quantity of acid in your blood (celled "metabolic acidosis"). Patients with liver disease or kidney disease or pregnant or breast-feeding patients should exercise particular caution and discuss this with their doctor.

FRAGMIN Solution for Injection 2,500 IU/0.2 ml, FRAGMIN Solution for Injection 5,000 IU (anti-Factor Xa)/0.2 ml, 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 multidose 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 product can be constituted with a solution that contains sodium. Tell your doctor if you or your child are following a low salt (sodium) diet.

3. How to use FRAGMIN Solution for Injection

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The quantity of FRAGMIN Solution for Injection you will be administered is determined for you individually.

FRAGMIN Solution for Injection is a solution for intravenous (IV) injection (into a vein) or subcutaneous (SC) injection (under the skin).

For the treatment of blood clots, FRAGMIN Solution for Injection is administered under the skin (subcutaneously).

If you need haemodialysis and haemofiltration (blood purification methods), FRAGMIN Solution for Injection will be administered into your vein or into the tubes of the dialysis machine.

FRAGMIN Solution for Injection must not be administered intramuscularly.

Treat the acute formation of blood clots in deep veins
If you are being treated for a blood clot in a deep vein, the injection will be given beneath the skin, usually in the abdominal area. You will receive either one injection of 200 IU/kg body weight (up to a maximum of 18,000 IU), or two injections of 100 IU/kg of body weight per day.

Your doctor may tell you to start taking another oral medicine to prevent blood clots, such as warfarin tablets.

Prevent clotting in blood dialysis and filtration equipment in patients with acute kidney failure or chronic kidney disease

- Patients with chronic renal insufficiency or patients with no known risk of bleeding
  - Haemodialysis and haemofiltration up to a maximum of 4 hours
    If you are undergoing haemodialysis and haemofiltration (blood purification methods), for a maximum duration of 4 hours, a single bolus injection of 5,000 IU may be performed in your vein or in the tube of the dialysis machine. Alternatively, administer 30 to 40 IU/kg total body weight IV bolus injection, followed by 10 to 15 IU/kg/h IV infusion.

    Your doctor may adjust the dose from one session to the next. The dose may be increased or decreased in steps of 500 or 1,000 anti-Factor Xa IU until a satisfactory outcome is obtained.

    The quantity injected will be determined on the basis of the illness for which you are being treated. If you have questions about the dose to be taken, ask your doctor.

- Haemodialysis and haemofiltration longer than 4 hours
  If you are undergoing haemodialysis and haemofiltration (blood purification methods) for longer than 4 hours, you will be given 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
  You will be given 5 to 10 IU/kg total body weight as IV bolus injection, followed by 4 to 5 IU/kg/h IV infusion.

Prevent blood clotting (coagulation) when surgery is performed
If FRAGMIN Solution for Injection is given to prevent blood clotting (coagulation) during surgery, the dose will depend on the type of operation.

- General surgery
  You will first be given a subcutaneous injection of 2,500 IU FRAGMIN Solution for Injection, within 2 hours before the operation. After the operation, you will receive an injection of 2,500 IU every morning until you are mobile again, usually for 5-7 days, and sometimes longer.

- General surgery associated with additional risks factors for thromboembolism (e.g., malignancy)
  Your doctor may give you FRAGMIN Solution for Injection by one of the regimens listed below:
  - Start on day before surgery
    5,000 IU SC on the evening before surgery. Following surgery, 5,000 IU SC each evening until you are mobile again, usually for 5-7 days, and sometimes longer.

  - 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 until you are mobile again, usually for 5-7 days, and sometimes longer.

- Orthopaedic surgery
  Your doctor may give you FRAGMIN Solution for Injection by 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, for up to 5 weeks.

  - 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, for up to 5 weeks.

  - 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.

Prevent clotting in those at risk when mobility is restricted during acute illness
You will be given 5,000 IU of FRAGMIN Solution for Injection subcutaneously (SC) once daily, generally for 12 to 14 days, or longer in case of continued restricted mobility.

Treat unstable coronary artery disease
You will be given 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.

Your doctor will continue treatment until you are clinically stable (generally at least 6 days), or longer if considered of benefit by the doctor. Your doctor might tell you to take aspirin as well.

If you are going to have revascularization procedure to restore blood flow, you will be given FRAGMIN Solution for Injection until the revascularization procedure is performed. The total treatment period should not exceed 45 days. The dose of FRAGMIN Solution for Injection is selected according to your 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.

Treat symptomatic blood clots to prevent recurrence of the clots in patients with cancer

- Month 1: You will be given FRAGMIN Solution for Injection 200 IU/kg body weight subcutaneously once per day for the first 30 days of treatment, depending on your body weight. The total daily dose should not exceed 18,000 IU per day.
- Month 2 to 6: FRAGMIN Solution for Injection should be administered subcutaneously, once per day, at a dose of approximately 150 IU/kg, depending on your weight. The total daily dose should not exceed 18,000 IU per day.
- If you have decreased blood platelet count (thrombocytopenia) or renal failure, doctor may reduce the dose of FRAGMIN Solution for Injection.

If you experience any side effects, talk to your doctor.

If you take more FRAGMIN Solution for Injection that you should

If you have accidentally injected too much FRAGMIN Solution for Injection, or if you have been administered too much FRAGMIN Solution for Injection by somebody else, immediately consult your doctor.

The possible symptoms of overdose are:

- Drowsiness, mental confusion, dizziness.
- Rash (spots), maculopapular rash (red spots and pimples) or erythematosis (red spots or patches).
- Nausea, vomiting, diarrhoea.
- Rarely, hyponatraemia (low blood sodium levels) and hyperkalaemia (high blood calcium levels).

Electrolyte (salts) imbalance and dehydration may also occur.

If you forget to use FRAGMIN Solution for Injection

Do not take a double dose to make up for a forgotten dose.

If you stop using FRAGMIN Solution for Injection

Always consult your doctor if you are considering stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

An allergic reaction (hypersensitivity) is a rare side effect (between 1 and 10 people in 10,000) but can be extremely severe (anaphylactic reaction), and even fatal. If you notice the rapid appearance of discomfort after administration of the medicine or if rapid swelling of the face and throat (angioedema) occurs, which may block your breathing, contact a doctor immediately.

There is a frequent risk of bleeding. The risk depends on the dose, and most bleeding is mild to moderate. However, cases of very severe, sometimes fatal, bleeding (haemorrhage) have been observed since the product was placed on the market. A haemorrhage can occur anywhere, including inside the skull or in the abdomen (stomach). The frequency of occurrence is not known. If you notice any significant bleeding, see your doctor immediately.

Common side effects (may affect between 1 and 10 people in 100)
- A decreased number of platelets (cells that promote blood clotting) in the blood (mild type I thrombocytopenia).
- Bleeding.
- A temporary increase in substances produced by the liver (transaminases).
- Redness of the skin or redness and pain at the injection site.

Uncommon side effects (may affect up to 1 in 100 people):
- Hypersensitivity.

Rare side effects (may affect up to 1 in 1,000 people)
- Localised destruction of the skin (skin necrosis).
- Transient hair loss.

Side effects of unknown frequency (cannot be estimated from the available data)
- A decrease in the number of immunologically-mediated and heparin-induced platelets (type II thrombocytopenia).
- Allergic reaction (anaphylaxis).
- Bleeding inside the skull or the abdominal cavity.
- Skin rash.
- Bruising (haematoma) around the spinal or epidural column.
- Rare increase in blood potassium levels (hyperkalaemia), especially in patients with chronic renal failure and diabetes mellitus (see section 2 “Warnings and precautions”).
- Risk of skeletal demineralisation resulting in brittle bones (osteoporosis) cannot be excluded.

Additional side effects in children
The side effects expected in children appear to be identical to those observed in adults. However, there is little information on possible long-term side effects in children.

Reporting of side effects
If you experience any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store FRAGMIN Solution for Injection

Keep this medicine out of the sight and reach of children.

Store below 30°C. Do not freeze. Do no use after the expiry date printed on label.

FRAGMIN Solution for Injection 10,000 IU (anti-Factor Xa)/ml (10 ml multidose vial) should not be used later than 14 days after first opening of the vial. Discard any unused solution 14 days after first penetration of the multidose vial.

6. Contents of the pack and other information

What FRAGMIN Solution for Injection contains

- The active substance is dalteparin sodium, and the quantity is specified in international units (IU) of anti-Factor Xa.
  - FRAGMIN Solution for Injection syringe 2,500 IU (anti-Factor Xa)/0.2 ml:
    Each syringe of 0.2 ml contains 2,500 IU (anti-Factor Xa) dalteparin sodium, or 12,500 IU/ml.
  - FRAGMIN Solution for Injection syringe 5,000 IU (anti-Factor Xa)/0.2 ml:
    Each syringe of 0.2 ml contains 5,000 IU (anti-Factor Xa) dalteparin sodium, or 25,000 IU/ml.
  - FRAGMIN Solution for Injection multidose vial 10,000 IU (anti-Factor Xa)/1 ml:
    Each vial of 10 ml contains 100,000 IU (anti-Factor Xa) dalteparin sodium.

- The other ingredients (excipients) are:
  - FRAGMIN Solution for Injection syringe 2,500 IU (anti-Factor Xa)/0.2 ml contain:
    Sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.
  - FRAGMIN Solution for Injection syringe 5,000 IU (anti-Factor Xa)/0.2 ml contain:
    Sodium hydroxide, hydrochloric acid and water for injection.
  - FRAGMIN Solution for Injection multidose vial 10,000 IU (anti-Factor Xa)/1 ml contain:
    Benzyl alcohol as preservative, sodium hydroxide, hydrochloric acid and water for injection.

What FRAGMIN Solution for Injection looks like and contents of the pack

- 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.

- Solution for injection 10,000 IU (anti-Factor Xa)/ml, multidose vial, 1x10 ml.
  A clear, colorless or straw-colored solution.

Single dose pre-filled syringes (Type I glass) are supplied 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 2 “Warnings and precautions”).

Not all presentations may be available in the market.

Manufacturer
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