Package leaflet: Information for the user

Fragmin® 100,000 IU/4 ml Multidose Vial
dalteparin sodium

Read all of this leaflet carefully before you start using this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Fragmin is and what it is used for

Fragmin contains the active ingredient dalteparin sodium. It is available in one strength: 100,000 IU (International Units)/4 ml Solution for injection.

Fragmin belongs to a group of medicines called low molecular weight heparins or antithrombotics, which help prevent the formation of blood clots by thinning the blood.

- Fragmin is used in adults above 18 years old to treat blood clots (venous thromboembolism).
- Venous thromboembolism is a condition where blood clots develop in the legs (deep vein thrombosis) or the lungs (pulmonary embolism), e.g. after surgery or prolonged bed-rest.

Fragmin is indicated in children for:

- Treatment of blood clots in the veins (venous thromboembolism or VTE) in children and adolescents 1 month of age and older.

Ask your doctor if you are unsure why you have been given Fragmin.

2. What you need to know before you are given Fragmin

You should not be given Fragmin:

- if you are allergic (hypersensitive) to the active ingredient dalteparin sodium or a similar product or any of the other ingredients of this medicine (listed in section 6).
- if you have an active stomach or ulcer of the duodenum (small intestine).
- if you have suffered from a brain haemorrhage (bleeding in your brain).

• if you suffer from any condition which may cause you to bleed more easily (e.g. haemophilia, liver failure). Ask your doctor if you are unsure.
• if you have a condition called septic endocarditis (an infection and inflammation of the lining of the heart and heart valves). Your doctor will have told you if you have this.
• if you have had a condition called "heparin-induced thrombocytopenia" (a decrease in the number of clotting cells (platelets) in your blood caused by heparin, which may cause you to bruise and bleed more easily). Your doctor will have told you if you have this.
• if you have an injury to, or have had an operation involving your spine, head, eyes or ears.

If you are receiving Fragmin to treat blood clots, you should not have a local, spinal or epidural anaesthetic.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you take Fragmin:
• if you have conditions which make you more susceptible to bleeding e.g.:

- after an operation or trauma
- a stroke caused by a bleed
- severe liver or kidney failure
- abnormal or low numbers of platelets (clotting cells)
- eye disease caused by blood pressure or diabetes
- taking other medicines that thin the blood (e.g. aspirin, warfarin, dipyridamole)
- uncontrolled high blood pressure.

• if you have been told by your doctor that you have a lot of potassium in your blood or have a low blood pH. Your doctor will monitor your blood regularly before and during treatment.
• if you have ever had an operation to insert an artificial heart valve.
• if you need any other injections.

You may need to have blood tests to monitor the effects of Fragmin:

- if you have kidney failure or liver problems
- if you are very thin or morbidly obese
- if you are pregnant
- if you are at increased risk of bleeding or rethrombosis (more blood clots)
- if you are a child.

Children and adolescents
Fragmin is not used for new born babies under 1 month of age.

Fragmin products that contain benzyl alcohol should not be used for more than one week in young children (between 1 month and 3 years old), unless advised by the doctor (see section "Fragmin contains benzyl alcohol and sodium").

Other medicines and Fragmin
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or are planning to take or use any other medicines. This includes medicines that you have bought for yourself.

Some medicines can affect the way Fragmin works, or Fragmin itself can reduce the effectiveness of other medicines taken at the same time.

Medicines that **increase** the effect of Fragmin include:

• Those used to thin your blood (e.g. aspirin, dipyridamole, glycoprotein receptor antagonists and warfarin)
• Medicines called non-steroidal anti-inflammatory drugs (NSAIDs) used to reduce pain and inflammation (e.g. indometacin)
• Some medicines for gout (e.g. sulfinpyrazone and probenecid)
• Etacrynic acid (a water retention tablet (diuretic))
• Solutions given to increase the blood volume (e.g. dextrans)
• Medicines known as cytostatics (used in cancer treatment)
• Thrombolytic medications for treating transmural heart attack (e.g. TPA-tissue plasminogen activator).

Medicines that can **reduce** the effect of Fragmin, include:
• Those for allergy and hay fever (e.g. antihistamines)
• Those used for heart or circulation problems (e.g. digoxin or digitoxin)
• Antibiotics known as tetracyclines which are used to treat bacterial infections
• Vitamin C (e.g. some vitamin supplements).

Other medicines that may interfere with Fragmin include:
- Those used to treat angina (e.g. intravenous nitroglycerine)
- Antibiotics such as high dose penicillin which are used to treat bacterial infections
- Anti-malarials (e.g. quinine)
- Tobacco smoking.

Please tell your doctor or pharmacist if you are taking or have recently taken any other low molecular weight heparins or anti-thrombotics.

Please note that if you are being treated with Fragmin for unstable coronary artery disease your doctor may adjust your dose of aspirin accordingly.

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

Pregnancy
Fragmin 100,000 IU (anti-Xa)/4 ml Multidose Vial contains benzyl alcohol, a preservative that may cross the placenta. It is recommended to use one of the Fragmin products that does not contain benzyl alcohol for the treatment of pregnant women (see "Fragmin contains benzyl alcohol and sodium").

Fragmin has not been found to cause harmful effects during pregnancy. The possibility of harm to the baby appears remote.

Fragmin is not recommended for the prevention of blood clots on artificial heart valves during pregnancy. Your doctor will discuss this with you.

If you are receiving Fragmin to treat blood clots, you should not have a local, spinal or epidural anaesthetic.

Breast-feeding
Fragmin 100,000 IU (anti-Xa)/4 ml Multidose Vial contains benzyl alcohol, a preservative that can pass into breast milk. It is recommended to use one of the Fragmin products that does not

contain benzyl alcohol for the treatment of breastfeeding women (see "Fragmin contains benzyl alcohol and sodium").

Fragmin contains benzyl alcohol and sodium
Fragmin 100,000 IU (anti-Xa)/4 ml Multidose Vial contains benzyl alcohol.

Fragmin products that do not contain benzyl alcohol are available.

Benzyl alcohol may cause allergic reactions. Benzyl alcohol has also been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children. The Fragmin products containing benzyl alcohol must not be given to newborn babies (up to 4 weeks old), unless recommended by the doctor. The Fragmin products containing benzyl alcohol must not be used for more than a week in young children (less than 3 years old), unless advised by the doctor. Taking large amounts of these Fragmin products may cause a build-up of benzyl alcohol in your body resulting in an increased amount of acid in your blood (called "metabolic acidosis"). Patients with liver or kidney disease and patients who are pregnant or breastfeeding need to be especially cautious and discuss with their doctor.

Fragmin 100,000 IU (anti-Xa)/4 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 may be prepared with a solution that contains sodium. Tell your doctor if you or your child are on a low salt (sodium) diet.

Driving and using machines
Fragmin does not affect the ability to drive and operate machinery.

3. How Fragmin is given to you

Your medicine will usually be administered by a doctor or nurse. The amount of Fragmin you receive will depend on your particular condition and the amount of Fragmin you receive will depend on your body weight.

Fragmin is given as a subcutaneous injection, which means it is injected beneath the skin. It is usually injected into a skin fold in your abdomen (stomach), or the outer aspects of your thigh. It should not be injected into your muscles.

Use in adults and the elderly
The recommended dose is 200 IU for each kg of body weight and may be given once a day (with a maximum daily dose of 18,000 IU), or 100 IU/kg twice a day. Your doctor will work out the right dose for you. If you have an artificial heart valve, the normal dose for prevention of blood clots is not sufficient. Your doctor will discuss this with you. Fragmin can be used together with other blood thinning medicines known as Vitamin K antagonist. Should this be desired, a minimum of five days would be required.

Medical staff may take blood samples during your treatment to monitor the effects of Fragmin.

Use in Children and Adolescents
Treatment of blood clots in the veins (Symptomatic Venous Thromboembolism - VTE)
The recommended dose depends on the child's body weight and age group and will be calculated by your doctor. Your doctor will advise you about the individualised dose of Fragmin according

to these criteria. Do not change the dosage and treatment schedule without consulting your doctor.

The following table shows the recommended starting dose for children and adolescents depending on their age:
Children 1 month to less than 2 years: 150 IU/kg twice daily.
Children 2 years to less than 8 years: 125 IU/kg twice daily.
Children 8 years to less than 18 years: 100 IU/kg twice daily.

The effect of Fragmin will be monitored after the initial dose and subsequent dose adjustment made using a blood test.

How to Inject Fragmin
Fragmin is administered under the skin (subcutaneously). This section of the leaflet explains how you should inject Fragmin to yourself or to your child. You should follow these instructions only after you have been trained by your doctor. If you are not sure what to do, talk to your doctor immediately. You should inject (or give) the dose of Fragmin at the times recommended by your doctor.

When dilution is required before administering Fragmin to children, it should be performed by a healthcare professional. You should follow your doctor's instructions on how and when to inject the diluted drug that is provided to you.

Please follow the steps explained below

Step 1: How you prepare your syringe for injection will depend on specific Fragmin presentation that you will be using

If you are using Fragmin from a vial:
Collect together the items that you need: vial, syringe, alcohol swab or soap and water. The vial, syringe and needle all have protective covers. The flip-off cap on the vial can rotate; this is normal. Check that all the covers are on firmly and if they are not on properly, do not use them. If a needle is bent do not use it.

Before you begin, make sure you know how much you are going to inject. Your doctor should have instructed you on the proper amount of solution to be administered. If the doctor has not given this instruction, please contact him/her.

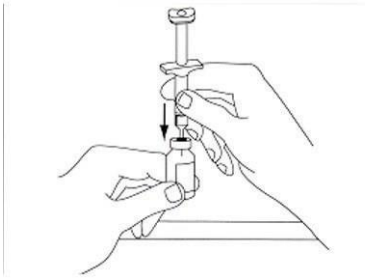
Prepare the medication dose*:* Remove the plastic top from the top of the vial (if present). Do not remove the rubber stopper or aluminium ring around the top of the vial. Clean the rubber stopper of the vial with an alcohol swab. After cleaning, do not touch the stopper with your hands or allow it to touch any surface (see Figures 1 and 2).

Figure 1

Figure 2

Draw the correct dose from the vial: Remove the syringe from the plastic or paper cover. Remove the cap covering the needle. Be careful not to touch the needle. With the vial in an upright position, push the needle straight down at a 90 degree angle into the vial stopper. Be careful not to bend the needle (see Figure 3).

Figure 3

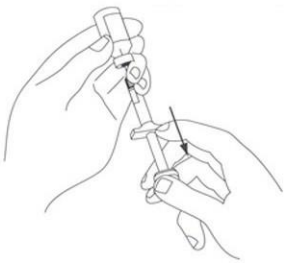


Turn the vial upside down, keeping the needle attached to the syringe in the vial. The needle and syringe will be pointing upward (see Figure 4).

Figure 4

Make sure that the tip of the needle is completely covered by the medication. Pull back on the syringe plunger to the correct dose of medication checking the dose level markings on the side of the syringe barrel (see Figure 5).

Figure 5



Keep the vial upside down, with the needle in the vial pointed upward. Tap the syringe, or "flick" it with your fingertips. This helps move bubbles to the top of the syringe (see Figure 6).

Figure 6

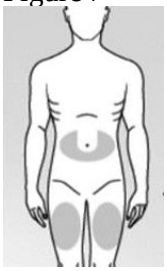
Once the bubbles are at the top of the syringe, gently push on the plunger to force the bubbles out of the syringe and back into the vial. Pull back slowly on the syringe plunger again to the correct dose, avoiding bubbles.
After removing the bubbles, check the amount of drug in the syringe according to the dose markings on the side of the syringe barrel to make sure it is correct.

You are now ready to inject. Continue to Step 2.

Step 2: Choosing and preparing the subcutaneous injection area

Choose one of the recommended injection sites below (see shaded areas Figure 7):
A "U" shaped area around the navel.
Side of the middle thighs.

Figure 7

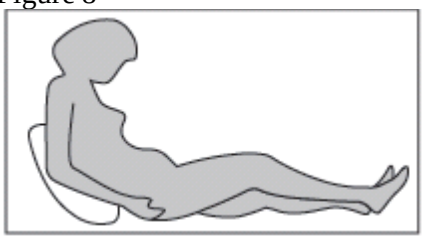


- Use a different site to inject each time a dose is given.
- Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars.
- If you or the child have psoriasis, do not inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skin lesions").

- Wash and dry your hands.
- Clean the injection site with a new alcohol swab, using a circular motion. Allow the skin to dry thoroughly. Do not touch this area again before giving the injection.

Step 3: Getting the right position
You or your child should be sitting or lying down for subcutaneous injection administration. If you are self-injecting, get yourself in a comfortable sitting down position where you can see your stomach (see Figure 8).

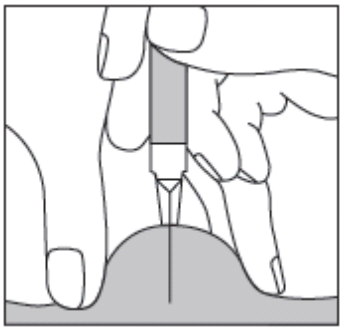
Figure 8



Step 4:
Using the thumb and forefinger, lift up a fold of skin with one hand. With the other hand, hold the syringe like a pencil. This will be the injection site.

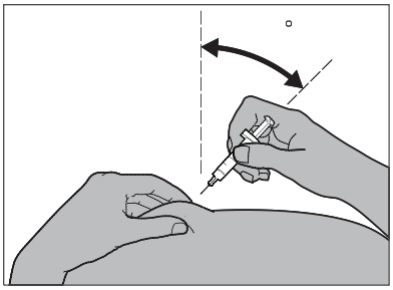
Step 5:
If you are injecting Fragmin to an adult or yourself, hold the syringe above the folded skin keeping it at a right angle (i.e. vertically as in the diagram and not at an angle). Insert the needle into the skin until the needle is fully inserted (see Figure 9).

Figure 9



If you are injecting Fragmin to a child, push the needle all the way into the skin with a quick, short motion, at an angle between 45° and 90° (see Figure 10).

Figure 10

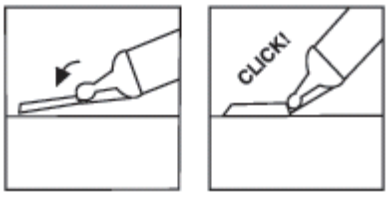


Step 6:
Push the plunger all the way down at a slow, steady rate to deliver the correct dose. Keep pinching the fold of skin while you are injecting and then release the fold of skin and pull the needle out.

If there is any oozing of blood at the injection site, apply gentle pressure. Do not rub the injection site as this may encourage bruising.

Press a cotton ball over the injection site for 10 seconds. Slight bleeding may occur. Do not rub the injection site. You may place a bandage over the injection site.

Step 7: If your syringe has a needle trap, activate the needle-trap
Place the plastic catcher against a hard, stable surface and with one hand pivot the syringe barrel upwards against the needle forcing the needle into the catcher where it locks in place.
Continue bending the needle until the syringe exceeds a 45-degree angle with the flat surface to render it permanently unusable.



Step 8:
Dispose of the syringe and needle into a sharps container. Keep your sharps bin out of reach of other people. When the sharps bin is almost full, dispose of it as instructed or speak to your doctor or nurse.

It is recommended that benzyl alcohol-free formulations are used in paediatric patients. Benzyl alcohol-free formulations are available.

If you are given more Fragmin than you should
If you feel that you have been given more Fragmin than you should, inform your doctor or nursing staff immediately. Your doctor may initiate measures to decrease the risk of bleeding.

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

4. Possible side effects

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

Stop using Fragmin and talk to a doctor or nurse at once if you get any signs of a severe allergic reaction (such as difficulty breathing, swelling of the lips, mouth, throat or eyes)

- Common side effects (may affect up to 1 in 10 people):

- A reversible decrease in the number of clotting cells (platelets) in your blood (Type I thrombocytopenia). This may make you bruise more easily.
- Bleeding at any site
- Certain substances produced by your liver may increase
- Pain and reactions at the site of injection
- Haematoma – collection of blood under the skin

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

  - Increased levels of potassium in your blood (symptoms may include temporary muscle weakness, loss of feeling and changes in your heartbeat)
  - Red skin rash and itchiness
  - Itching
  - Allergic reactions
  - Your bones may weaken and break more easily. This is known as osteoporosis and has been seen in patients using heparin for a long time

- Rare side effects (may affect up to 1 in 1,000 people):

  - An immune system problem resulting in a severe decrease in the number of clotting cells (platelets) in your blood (Type II thrombocytopenia)
  - Alopecia (hair loss)
  - Painful skin lesions

- Not known (frequency cannot be estimated from the available data):

  - Bleeding inside or around your brain, symptoms may include sudden severe headache
  - Bleeding behind your abdomen (stomach), symptoms may include a feeling of tenderness and swelling around your stomach
  - Bruising of the spine which may lead to back pain, tingling, numbness or weakness in your legs, bowel or bladder problems

If you have an artificial heart valve, treatment with Fragmin might not be sufficient to prevent a blood clot, and you might develop a clot in the heart valve.

The adverse reactions in children are expected to be the same as in adults, however there is only a little information about the possible side effects of long term use in children.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fragmin

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

Fragmin 100,000 IU (anti-Xa)/4 ml Multidose Vial: diluted solution is stable for 48 hours at 25°C.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Fragmin should not be used after the expiry date which is printed on the label and carton. The expiry date refers to the last day of that month.
The vial may be used to give a number of doses, but once the vial has been opened the solution should be used within 14 days.

Store below 30°C.
Your doctor or nurse will store Fragmin in a safe place under the above conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Fragmin contains
The active ingredient in Fragmin is dalteparin sodium.
Each vial contains a total of 100,000 IU (International units) of dalteparin sodium in 4 ml of solution, that is 25,000 IU in each ml of solution.
The other ingredients are benzyl alcohol (14 mg/ml) and water for injections.

Fragmin 100,000 IU/4 ml vials contain benzyl alcohol as a preservative. See section "Fragmin contains benzyl alcohol and sodium".

What Fragmin looks like and contents of the pack
Fragmin 100,000 IU/4 ml multidose vial is a clear, colourless or straw coloured solution. Each pack contains 1 vial.

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