Package leaflet: Information for the user

Nadroparin Calcium Aspen Forte 19,000 I.U. anti-Xa/ml solution for injection in a pre-filled syringe
Nadroparin Calcium Aspen Forte 15,200 I.U. anti-Xa/0.8ml solution for injection in a pre-filled syringe
Nadroparin Calcium Aspen Forte 11,400 I.U. anti-Xa/0.6ml solution for injection in a pre-filled syringe

Nadroparin calcium

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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nadroparin Calcium Aspen Forte is and what it is used for

Nadroparin Calcium Aspen Forte is an antithrombotic medicine belonging to the class of low-molecular weight heparins.

Nadroparin Calcium Aspen Forte is used for:
Treatment of deep venous thrombosis.

2. What you need to know before you use Nadroparin Calcium Aspen Forte

Do not use Nadroparin Calcium Aspen Forte:
- if you are allergic to nadroparin calcium, to heparin or any of the other ingredients of this medicine (listed in section 6)
- with existing or a history of known heparin-induced decrease in the number of blood platelets (thrombocytopenia Type II) or a history of decrease in the number of platelets due to nadroparin calcium.
- with organ lesions that may have a tendency to bleed, such as:
  - acute gastro-intestinal ulcers
  - cerebral haemorrhage
  - vasodilatation (aneurism) in the brain
- with blood clotting disorders (tendency to bleed, lack of clotting factors, with pronounced decrease in the number of platelets)
- if you have a stroke that is caused by bleeding in the brain
- with severe, unmanageable high blood pressure
- with severe impairment of the liver function
- with severe impairment of the kidney function (creatinine clearance < 30 ml/min)
- if you have infective endocarditis (inflammation of the inner lining of the heart)

- with injuries of and surgical procedures on the central nervous system as well as the eyes and ears
- with bleeding in the eye or other active bleeding processes
- with disorders of the retina (retinopathies), vitreous haemorrhage
- with miscarriage (abortus imminens)
- with regional anaesthesia (spinal or epidural anaesthesia), lumbar puncture)

Warnings and precautions
Talk to your doctor or pharmacist before using Nadroparin Calcium Aspen Forte:
- if you have a low blood platelet count (thrombocytopenia) and platelet function disorders
- if you have disorders of the kidney, liver and pancreas
- if you have uncontrollable high blood pressure (hypertension)
- if you have a history of peptic ulcers
- if you have suspected malignancies with tendency to bleed
- if you have vascular diseases of the eyes
- after recent brain, spinal cord or eye surgery
- if you have kidney or ureteral stones
- in case of simultaneous use of medicines that increase blood potassium concentrations as well as simultaneous use of anticoagulants or platelet inhibitors (for instance acetylsalicylic acid)
- in case of high-dosage nadroparin calcium treatment in patients who recently underwent surgery
- in patients older than 65 years of age
- in patients younger than 18 years of age

The use of Nadroparin Calcium Aspen Forte is not recommended in patients who underwent surgery within the last 5 days.

Because of the risk of heparin-induced thrombocytopenia, the platelet count should be checked regularly during treatment with Nadroparin Calcium Aspen Forte.

Checking the platelet count is recommended prior to initiating treatment, during the first day of treatment and subsequently every three to four days, as well as at the end of treatment.

Occasionally, a mild transient thrombocytopenia (Type I) with platelet counts between 100,000/microliter and 150,000/microliter (caused by transient platelet activation) occurs at the beginning of treatment. Complications generally do not occur in these cases. Treatment may, therefore, be continued.

Antibody-mediated severe thrombocytopenia (Type II) with platelet counts clearly below 100,000/microliter or a rapid drop to less than 50% of the initial value is rarely observed. In non-sensitized patients, platelet count decrease primarily starts 6 to 21 days after the onset of treatment; in sensitized patients, platelet count decrease may start within hours. The severe form of thrombocytopenia may be associated with arterial and venous thrombosis/thromboembolism, disseminated intravascular coagulation, and possible skin necrosis at the injection site, petechiae**,** purpura and melena. In such cases, Nadroparin Calcium Aspen Forte must be discontinued immediately and a different antithrombotic treatment must be considered. The patient must be informed that he or she may no longer use heparin-containing medications in the future.

Heparin may suppress adrenal secretion of aldosterone, which can lead to hyperkalaemia particularly in patients with elevated potassium plasma concentrations or in patients at risk for elevated potassium plasma concentrations, such as patients with diabetes mellitus, persistent renal function impairment, pre-existing metabolic acidosis, or in patients taking drugs that increase potassium plasma concentrations (for instance ACE inhibitors, non-steroidal anti-inflammatory drugs [NSAIDs]). The risk of hyperkalaemia appears to increase with duration of treatment, but is generally reversible. Plasma potassium concentrations should therefore be monitored in patients at risk.

If patients with renal impairment (see section 2. Nadroparin Calcium Aspen Forte should not be used) are treated for deep venous thrombosis, the laboratory test results should be monitored, preferably via

anti-Xa level determination (amidolytic method with chromogenic substrate). The anti-Xa activity can be checked during the 2nd and 4th day, following subcutaneous application and should lie in the range of 0.5 to 1.2 I.U. anti-Xa/ml.

In patients with mild to moderate renal impairment (creatinine clearance ≥ 30 and <60 ml/min), a dose reduction should be considered (see section 3. How to use Nadroparin Calcium Aspen Forte).

Note: Nadroparin Calcium Aspen Forte must not be injected into a muscle (i.m.) or into a vein (i.v.).

Due to risk of bruising during Nadroparin Calcium Aspen Forte treatment, intramuscular injection of other medications should be avoided.

In very rare cases, skin damage preceded by redness (purpura) or painful, inflamed (erythematous) skin, usually occurring at the site of injection, was observed. In these cases, treatment must be immediately discontinued.

As there are no compatibility studies available, the contents of the Nadroparin Calcium Aspen Forte prefilled syringe must not be mixed with other medicines.

Children and adolescents
There are insufficient clinical data for use of Nadroparin Calcium Aspen Forte in children. The use in children is therefore not recommended.

Elderly patients
Dosage adjustment in elderly patients is not necessary, except in case of impairment of the kidney function. It is recommended to monitor the kidney function in elderly patients prior to starting treatment.

Other medicines and Nadroparin Calcium Aspen Forte
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following medicines may increase the effects of Nadroparin Calcium Aspen Forte and increase the risk of bleeding:
- Medicines that inhibit blood clotting (oral anticoagulants)
- Acetylsalicylic acid (or other salicylates)
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Anti-platelet drugs
- Systemic adrenocortical hormones (glucocorticosteroids)
- Dextran

The interaction of heparin with intravenous nitroglycerin that can lead to a reduced efficacy of heparin also cannot be ruled out for Nadroparin Calcium Aspen Forte.

Medicines that increase blood potassium concentrations may only be used simultaneously with Nadroparin Calcium Aspen Forte under very close medical supervision.

Administration of Nadroparin Calcium Aspen Forte in patients, who are switched to oral anticoagulants, should be continued until a stable INR (International Normalized Ratio) in the desired range has been reached.

Please note that this information may also apply to recently administered medicines.

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.

Animal studies are insufficient with respect to reproductive toxicity. However, there is only limited clinical information on the extent to which the active substance passes into the placenta. There is also only limited clinical information on the use during pregnancy that has not shown adverse effects on the pregnancy or on the health of unborn or new-born babies. Due to the limited clinical experience, the use of Nadroparin Calcium Aspen Forte during pregnancy is not recommended.

There is insufficient information on the excretion of nadroparin calcium in breast milk. The use of Nadroparin Calcium Aspen Forte during breast-feeding is, therefore, not recommended.

Driving and using machines
There are no data on the effects on driving or the use of machines.

3. How to use Nadroparin Calcium Aspen Forte

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

Dosing
Depending on the dosage, the appropriate prefilled syringe volumes between 0.6 and 1.0 ml are to be used.

The prefilled syringes of 0.6 ml, 0.8 ml and 1.0 ml are graduated in 0.1 ml increments. For patients needing dosages of 0.4 ml, 0.5 ml, 0.7 ml or 0.9 ml, in accordance with their individual body weight, the correct dosage can be obtained by using the respective higher-dose prefilled syringe and discarding the excess amount of 0.1 or 0.2 ml before use.

Treatment of deep venous thrombosis
Nadroparin Calcium Aspen Forte should be injected subcutaneously once daily in a dosage adjusted to the patient's body weight (see Table below).

Weight in kg	**Treatment of deep venous thrombosis subcutaneous injection once daily Nadroparin Calcium Aspen Forte**
< 50	0.4 ml
50 to 59	0.5 ml
60 to 69	0.6 ml
70 to 79	0.7 ml
80 to 89	0.8 ml
≥ 90	0.9 ml

The administration of oral anticoagulants should be started on the first day. The duration of treatment with Nadroparin Calcium Aspen Forte is at least 5 days and should be continued until sufficient oral anticoagulation has been achieved.

How to use Nadroparin Calcium Aspen Forte
The prefilled syringe is intended for subcutaneous injection.

For subcutaneous administration of Nadroparin Calcium Aspen Forte the lateral abdominal wall is the usual site of injection. As an alternative, Nadroparin Calcium Aspen Forte can be injected into the thigh. The needle is inserted perpendicularly into a fold of the skin formed between the thumb and index finger that should be held gently but firmly until injection has been completed. The injection site should not be rubbed.

Duration of use
The duration of treatment is determined individually by the treating physician.

If you use more Nadroparin Calcium Aspen Forte than you should
In the treatment of deep venous thrombosis, prolongation of the activated Partial Thromboplastin Time (aPTT) value should only be considered as a sign of overdose. Dose-escalations aiming at a PTT prolongation bear the risk of an overdose or bleeding. Bleeding is the major sign of overdose. Monitoring of platelet count and other coagulation parameters is advised. Minor bleeding rarely requires specific therapy. Reducing or delaying the subsequent dose of Nadroparin Calcium Aspen Forte is usually sufficient. The administration of protamine sulphate should only be considered if the patient's condition is serious. The anti-coagulant effect of Nadroparin Calcium Aspen Forte is largely neutralized but some anti-Xa activity will remain (approximately 25%). 6 mg protamine sulphate neutralises about 950 I.U. anti-Xa nadroparin calcium.

If you forget to use Nadroparin Calcium Aspen Forte
Do not take a double dose to make up for a forgotten dose.

When an injection of Nadroparin Calcium Aspen Forte was forgotten, daily administration should still be continued immediately. Therefore, administration of two consecutive injections must not take place under any circumstance.

If you stop using Nadroparin Calcium Aspen Forte
To ensure reliable protection against thrombosis, it is necessary to administer the injections for the duration specified by the physician. If this is not possible, for instance due to the occurrence of adverse effects, please immediately consult with your doctor.

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

4. Possible side effects

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

Symptoms to which you must pay attention
Allergic reactions: These rarely occur when using Nadroparin Calcium Aspen Forte. The signs are:
- raised and itchy skin rashes (hives)
- swelling, sometimes in the face or mouth (angioedema), which cause breathing difficulties

Skin damage at the injection site.

Go to your doctor immediately, if you have any of these symptoms and discontinue using Nadroparin Calcium Aspen Forte

The following convention has been used for the classification of adverse reactions in terms of frequency:
Very common: more than 1 treated patient out of 10
Common: 1 to 10 treated patients out of 100
Uncommon: 1 to 10 treated patients out of 1,000
Rare: 1 to 10 treated patients out of 10,000
Very rare: less than 1 treated patient out of 10,000
Not known (cannot be estimated from the available data)

Side effects
So far, the following adverse reactions have been observed. Application experiences with nadroparin calcium show that in about 3% of the prophylactically treated patients had adverse reactions.

<u>Very common:</u>
- Blood clots (minor hematomas) at the injection site, in some cases with nodules (granulomas)
- bleeding at various sites

Common:
- Irritations at the injection site
- Open or hidden bleeding complications (particularly affecting the skin, mucous membranes, lesions, as well as the gastrointestinal tract and urogenital tract regions), which can lead to anaemia (haemorrhagic anaemia)
- Elevated liver values (aminotransferases, gamma-GT), LDH and lipase
- Increased calcium concentration in the blood serum

Uncommon:
- Mild, transient reduced platelet count (thrombocytopenia Type I) (See section 2. Warning and Precautions)

Rare:
- Calcium deposits at the injection site (calcinosis), particularly in patients with severe kidney function impairment
- Allergic reactions with symptoms such as nausea, vomiting, elevated body temperature, headache, hives (urticaria), itching (pruritis), difficulty breathing (dyspnoea), upper respiratory spasms (bronchospasm), hypotension
- Transient aldosterone deficiency (hypoaldosteronism)
- Mild, heparin-induced reduced platelet count (thrombocytopenia Type II) (See section 2. Warning and Precautions)
- High platelet count (thrombocytosis)
- Proliferation of white blood cells (eosinophilia)
- Anaphylactoid reactions, anaphylactic shock, angioedema
- Rash, skin reddening (erythema)
- Hair loss (alopecia)
- Skin damage (necrosis) at the injection site (See section 2. Warning and Precautions)

Very rare:
- Increased thrombocyte count (thrombocythemia) over 1,000,000/mm^3, mainly observed postoperatively
- Hypersensitivity reactions (including skin reactions)
- Persistent painful erection of the penis (priapism)

Not known:
- Headache
- Migraine

Cases of severe adverse drug reactions, such as bleeding in the brain and eye bleeding have been reported. Epidural bleeding in the lumbar region following catheterized spinal anaesthesia that can lead to paraplegia has been observed.

Bleeding
Bleeding is the major sign of overdose. Please tell your doctor if you experience problems/complications with bleeding.

Minor bleeding rarely requires specific therapy. Reducing or delaying the subsequent dose of Nadroparin Calcium Aspen Forte is usually sufficient.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system: HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971;*Fax; +353 1 6762517. Website: www.hpra.ie; Email: medsafey@hpra.ie*. By reporting side effects, you can help provide more on information on the safety of this medicinal product.

5. How to store Nadroparin Calcium Aspen Forte

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

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

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

Nadroparin Calcium Aspen Forte must not be mixed with any other preparations.

Do not use this medicine if you if you notice turbidity or discoloration of the solution.

Use only clear solutions for injections. For single use only, discard unused residual solution.

Store below 25°C.

6. Contents of the pack and additional information

What Nadroparin Calcium Aspen Forte contains
- The active substance is: Nadroparin calcium

Depending on the strength of your medicine prescribed for you:
1 ml solution for injection contains 19,000 I.U. anti-Xa nadroparin calcium (equivalent to 95 to 130 I.U. anti-Xa/mg).

1 Pre-filled syringe with 0.8 ml solution for injection contains 15,200 I.U. anti-Xa nadroparin calcium.

1 Pre-filled syringe with 0.6 ml solution for injection contains 11,400 I.U. anti-Xa nadroparin calcium

The other ingredients are: Calcium hydroxide/hydrochloric acid 10 % (for pH adjustment), water for injections.

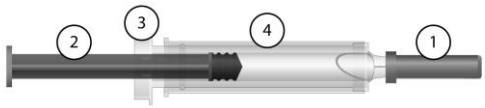
What Nadroparin Calcium Aspen Forte looks like and contents of the pack
The Nadroparin Calcium Aspen Forte prefilled syringe contains a clear to slightly opalescent, colourless or slightly yellowish solution. The cylindrical cavity is made of glass. The needle is made of stainless steel and is equipped with a protective cap that may contain natural rubber (latex). The moveable plunger consists of a blue synthetic material (for Nadroparin Calcium Aspen Forte® 0.6 ml and Nadroparin Calcium Aspen Forte®1.0 ml syringes or a purple synthetic material (for Nadroparin Calcium Aspen Forte® 0.8 ml prefilled syringes).

Nadroparin Calcium Aspen Forte is available in the following sizes:

Packs of 2, 6, 10, 20, 30 and 50 prefilled syringes each containing 0.6 ml solution for injection,
Packs of 2, 6, 10, 20, 30 and 50 prefilled syringes each containing 0.8 ml solution for injection,
Packs of 2, 6 and 10 prefilled syringes each containing 1.0 ml solution for injection,
Not all pack sizes may be marketed.

Step by step guide:
Parts of the Nadroparin Calcium Aspen Forte prefilled syringe:

① Needle guard
② Piston
③ Syringe handle
④ Safety sleeve



Instructions for use

1. Wash your hands thoroughly with soap and water and then dry them with a towel.

2. Take the syringe out of the carton and check:

- the expiration date located on the outer carton and on the pre-filled syringe
- if the syringe is opened or damaged

3. Sit or lie down comfortably

Select an area of skin in the lower abdominal region, at least 5 cm below the navel (Figure **A**).

Alternate the left and right injection site in the lower abdominal region at each injection. This helps to reduce possible discomfort at the injection site. If it is not possible to inject into the lower abdominal region, ask your doctor for advice.

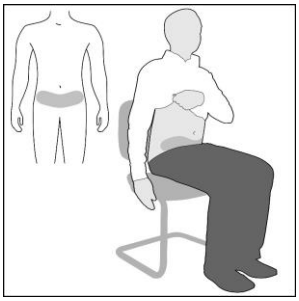


Figure A

4. Clean the injection area with an alcohol swab

5. Remove the needle guard, by turning it and then pulling it in a straight line from the syringe body (Figure **B**).

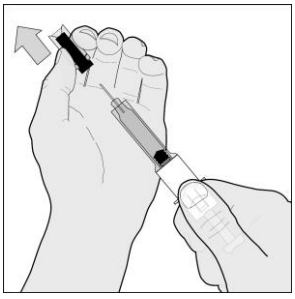


Figure B

Discard the needle guard.

If the volume of the syringe is greater than you need, you must remove the excess **before** you inject.

- Hold the syringe **vertical** so that the needle is pointing downwards.
- Push the piston gently downward until the **bottom** of the trapped air bubble **sits at** the mark with the volume that your doctor has prescribed for you.
- Allow the liquid that comes out of the needle to drop onto a tissue and discard it.
- The syringe is now ready for use.

Important note:

- **Do not touch the needle or allow it to come into contact with anything before the injection.**
- The presence of an air bubble in the prefilled syringe is normal. **Do not try to remove this air bubble before performing the injection** – you could otherwise lose some of the medicine.

6. Gently pinch the skin that has been cleaned to make a fold. Hold this fold between thumb and index finger during the entire injection (Figure **C**.)

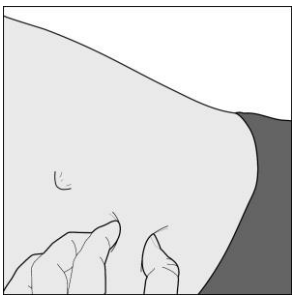


Figure C

7. Hold the syringe firmly by the syringe handle. Insert the full length of the needle at a right angle into the skin fold (Figure **D**).

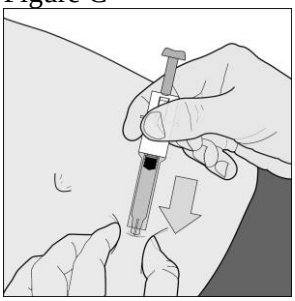


Figure D

8. **Inject ALL of the content in the prefilled syringe under the skin by pushing the plunger down as far as possible (**Figure **E**). Remove the syringe gently from the skin.

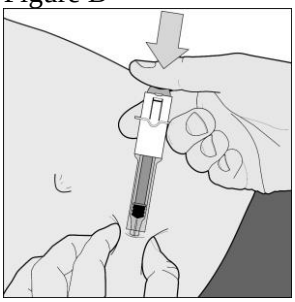


Figure E

9. After injection, hold the prefilled syringe by the safety sleeve with one hand. Use the other hand to firmly pull the syringe back. This unlocks the cylinder. Slide the cylinder over the syringe until it locks into place over the needle (Figure **F**).

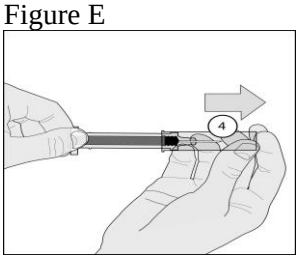


Figure F

Marketing Authorisation holder and Manufacturer:

Marketing Authorisation holder:
Mylan IRE Healthcare Limited
Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13, Ireland

Manufacturer:
Aspen Notre Dame De Bondeville, 1 rue de l'Abbaye, 76960 Notre Dame de Bondeville, France

This medicinal product is authorised in the Member States of the EEA under the following names:
Liechtenstein: Fraxiforte
Bulgaria, Czech Republic, Latvia, Lithuania, Slovakia, Slovenia, Spain: Fraxiparine Forte
Belgium, Luxembourg, France, Germany, Hungary, Italy, Netherlands, Poland, Portugal: Fraxodi

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