

Patient information leaflet: Information for the user
Nadroparin Calcium Aspen
3,800 I.U. anti-Xa/ 0.4 ml 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 is and what it is used for
2. What you need to know before you take Nadroparin Calcium Aspen
3. How to use Nadroparin Calcium Aspen
4. Possible side effects
5. How to store Nadroparin Calcium Aspen
6. Contents of the pack and other information

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

Nadroparin Calcium Aspen is an antithrombotic agent. It is a low-molecular weight heparin.

Nadroparin Calcium Aspen is used for

- Perioperative thrombosis prophylaxis,
 - Peri- and postoperative primary prophylaxis of deep vein thrombosis in patients with
 - o low, moderate or high thromboembolic risk,
 - o larger orthopaedic surgeries (e.g. elective hip surgeries),
- Treatment of deep vein thrombosis,
- Thrombosis prophylaxis and anticoagulation with extracorporeal circulation during haemodialysis and hemofiltration.

Note:

The medicinal product is available in different strengths which are not suitable for all therapeutic indications (see section 3. How to use Nadroparin Calcium Aspen).

2. What you need to know before you take Nadroparin Calcium Aspen

Do not use Nadroparin Calcium Aspen

- If you are allergic to nadroparin calcium, heparin or any of the other ingredients of this medicine (listed in section 6).
- In case of current or history of heparin-related drop in the platelet count (type II thrombocytopenia) or a drop in the platelet count with nadroparin calcium in the medical history
- In case of organ damage which can be susceptible to bleeding such as:

- Acute gastrointestinal ulcers
- Cerebral bleeding
- Distended vessel (aneurysm) in the brain
- In case of coagulation disorders (susceptibility to bleeding, coagulation factor deficiency, extensive reduction of platelet count)
- In case of stroke caused by bleeding in the brain
- In case of severe, uncontrollable hypertension
- In case of severe hepatic impairment
- In case of severe renal impairment (creatinine clearance < 30 ml/min.) except during haemodialysis treatment
- In case of infectious inflammation of the heart's inner layer (endocarditis)
- In case of injuries and surgical procedures of the central nervous system, and on the eye and ear
- In case of bleeding in the eye or other active bleeding processes
- In case of retinal disorders (retinopathies), vitreous body haemorrhage
- In case of imminent miscarriage
- In case of deep vein thrombosis: Regional anaesthesia (spinal or epidural anaesthesia), lumbar puncture

Warnings and precautions

Talk to your doctor or pharmacist before using Nadroparin Calcium Aspen if any of the following apply to you:

- Thrombocytopenia and platelet function disorders
- Renal, hepatic, and pancreatic dysfunction
- Uncontrollable high blood pressure (hypertension)
- Peptic ulcers in the medical history
- Suspected malignancies with susceptibility to bleeding
- Vascular disorders of the eyes
- In case of recent surgery on the brain, spinal cord or eye
- Kidney and/or ureteral stones
- Lumbar puncture
- Spinal or epidural anaesthesia
- Simultaneous use of medicines which increase the serum potassium level and with the simultaneous use of (oral) anticoagulants or platelet aggregation inhibitors (e.g. acetylsalicylic acid)
- High-dose nadroparin calcium treatment in recently operated patients
- Patients aged 65 years and older
- Patients aged 18 years and younger

Nadroparin Calcium Aspen should be taken with care and after careful individual risk-benefit analysis in patients with lumbar puncture, spinal or epidural anaesthesia who received preventive treatment with Nadroparin Calcium Aspen due to the risk of complications arising from bleeding which may lead to neurological deficits and complete paralysis of the limbs (paraplegia).

To date no results from randomized, controlled clinical studies are available which prove the safe use of higher doses of Nadroparin Calcium Aspen (for example, for deep vein thrombosis prophylaxis in patients with high thromboembolic risk) with the simultaneous use of anaesthetic methods applied close to the spinal cord. Patients must be under careful neurological monitoring after the application of anaesthesia close to the spinal cord, whereby especially persistent sensory and motor deficits must be noted, since Nadroparin Calcium Aspen may cause bleeding into the spinal cord at the injection site.

The platelet count must be checked at regular intervals during treatment with Nadroparin Calcium Aspen due to the risk of heparin-induced thrombocytopenia.

Checks of the platelet count are recommended prior to therapy, on day 1 of therapy, and then at regular intervals of three to four days as well as at the end of therapy.

Occasionally, mild, temporarily thrombocytopenia (type I) develops at the beginning of therapy (caused by temporary platelet activation) with a platelet count between 100,000/ μ l and 150,000/ μ l. Complications generally do not develop in these cases. Therefore, the treatment can be continued.

Rarely, antibody-induced severe thrombocytopenia (type II) develops with platelet counts of significantly below 100,000/ μ l or a fast drop to less than 50% of the initial value. The drop in the platelet level primarily starts 6 to 21 days after beginning treatment in non-sensitized patients, in sensitized patients this may occur within hours. The severe form of thrombocytopenia may be accompanied by arterial and venous thrombosis/thromboembolism, disseminated intravascular coagulation, possibly skin necrosis on the injection site, petechial bleeding, purpura, and melena. In these cases, Nadroparin Calcium Aspen must be immediately discontinued and a different antithrombotic treatment must be considered. The patient must be informed that s/he must not receive any heparin-containing medicinal products in the future.

Heparin can suppress the adrenal secretion of aldosterone which can cause hyperkalaemia, especially in patients with elevated plasma potassium level or in patients with a risk of an elevated plasma potassium level such as diabetes mellitus, persistent renal impairment, previously existing metabolic acidosis or the administration of medicinal products which increase the plasma potassium level (e.g. ACE inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs]). The risk of hyperkalaemia seems to increase with the duration of therapy, but usually is reversible. The plasma potassium level should be checked in risk patients.

If patients with renal failure (see section 2. Do not use Nadroparin Calcium Aspen) are treated due to deep vein thrombosis, the lab parameters should be monitored, preferably by measuring the anti-Xa level (amidolytic assay with chromogenic substrate). Anti-Xa activity can be checked on day 2 and day 4, about 3 hours after subcutaneous application, and should lie within the range of 0.5 to 1.2 I.U. anti-Xa/ml.

A reduction of the dose should be considered in patients with minor to moderate renal impairment (creatinine clearance \geq 30 and $<$ 60 ml/min.) (see section 3. How to use Nadroparin Calcium Aspen).

Note:

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

The intramuscular injection of other medicinal products should be avoided during therapy with Nadroparin Calcium Aspen due to the risk of hematoma development.

In very rare cases skin damage was observed, usually on the injection site, which was preceded by reddened (purpura) or painful, inflammatory (erythematous) skin spots. In these cases treatment should be immediately discontinued.

Since no compatibility studies are available, the content of the Nadroparin Calcium Aspen pre-filled syringe must not be mixed with other preparations.

Children and adolescents

There are no data on the use of Nadroparin Calcium Aspen in children. The use in children is therefore not recommended.

Elderly patients

A dose adaptation for elderly patients is not necessary unless in the presence of renal failure. It is recommended to check the kidney function in elderly patients prior to use.

Other medicines and Nadroparin Calcium Aspen

Please tell your doctor or pharmacist if you are taking/using or have recently taken/used any other medicines, even over-the-counter medicines.

This is particularly important because the simultaneous use of several medicines with Nadroparin Calcium Aspen may increase the risk of bleeding:

- (Oral) anticoagulants
- Acetylsalicylic acid (or other salicylates)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Platelet aggregation inhibitors
- Systemic adrenocortical hormones ([gluco-] corticosteroids)
- Dextran

The interaction of heparin with intravenous nitroglycerin which can reduce the effect of heparin can also not be excluded for Nadroparin Calcium Aspen.

Medicines which increase the serum potassium level must only be used under especially careful medical monitoring during the simultaneous use of Nadroparin Calcium Aspen.

The administration of Nadroparin Calcium Aspen in patients who are switched to oral anticoagulants should be continued until a stable INR (International Normalized Ratio) has been achieved within the desired range.

Please note that this information may also apply to medicinal products you have recently used.

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 testing showed no signs of a fetotoxic effect. However, only limited clinical data are available in how far the active substance passes into the placenta. Clinical experience about use during pregnancy is limited which show no adverse effects on pregnancy or the health of the foetus/new-born. Use of Nadroparin Calcium Aspen is not recommended during pregnancy due to limited clinical experience.

Only limited information is available whether nadroparin calcium is excreted into the breast milk. For this reason the use of Nadroparin Calcium Aspen is not recommended while breastfeeding.

Driving and using machines

No studies on the effects on the ability to drive or use machines have been performed.

3. How to use Nadroparin Calcium Aspen

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

Dosing

Depending on the dose the corresponding fillings between 0.4 to 1.0 ml are to be applied.

The syringes that contain 0.6 ml, 0.8 ml and 1.0 ml have graduations of 0.1 ml increments. For patients with an indication of "treatment of deep vein thrombosis" who require doses of 0.5 ml, 0.7 ml or 0.9 ml according to their individual body weight the correct dose can be maintained by using a higher dosed pre-filled injection after removing the excess amount of 0.1 ml before use.

Perioperative thrombosis prophylaxis

Peri- and postoperative primary prophylaxis of deep vein thrombosis

- In patients with low, moderate or high thromboembolic risk

0.3 ml (2,850 I.U. anti-Xa) subcutaneous 2 hours before surgery. Afterwards, 0.3 ml (2,850 I.U. anti-Xa) subcutaneously every morning until the patient is fully mobilized, but at least for the duration of 7 days.

- In patients with larger orthopaedic surgeries (e.g. elective hip surgeries)

The initial doses should be administered 12 hours before and 12 hours after the surgery. These doses and the following single daily doses should be modified to fit the body weight in accordance with the scheme below. Treatment should be continued as long as there is the risk of thrombosis, but at least for 10 days.

Larger orthopaedic procedures such as elective hip surgeries s.c. injection once daily		
Weight in kg	Preoperative and postoperative for 3 days	From the postoperative day 4
< 50	0.2 ml	0.3 ml
50 to 69	0.3 ml	0.4 ml
≥ 70	0.4 ml	0.6 ml

Treatment of deep vein thrombosis

Nadroparin Calcium Aspen should be subcutaneously injected twice daily (every 12 hours) at a dose adapted to the patient's body weight (see following table).

Weight in kg	Treatment of deep vein thrombosis s.c. Injection 2-times daily
< 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 from day 1. The duration of the treatment with Nadroparin Calcium Aspen is at least 5 days and should be continued until sufficient oral anticoagulation has been achieved.

Anticoagulation during haemodialysis and hemofiltration

The dose must be individually adapted to each patient. Nadroparin Calcium Aspen is usually administered into the femoral artery at the beginning of the dialysis as a single dose. The following table indicates the recommended initial doses for patients without increased risk of bleeding. An additional, lower dose may be administered during dialysis which takes longer than 4 hours. The dose should be modified in the following dialysis sessions depending on the results of the first dialysis session.

Weight in kg	Coagulation inhibition during haemodialysis and hemofiltration in the femoral artery at the beginning of dialysis
< 50	0.3 ml
50 to 69	0.4 ml
≥ 70	0.6 ml

How to use Nadroparin Calcium Aspen

The pre-filled syringe is intended for subcutaneous injection.

The lateral abdominal wall is the usual injection site for the subcutaneous application of Nadroparin Calcium Aspen; alternatively, Nadroparin Calcium Aspen can be injected into the thigh.

The injection needle is vertically injected into a skin fold formed by thumb and index finger; this must be carefully, but firmly held until the injection is completed. The injection site should not be massaged.

Nadroparin Calcium Aspen is injected into the femoral artery during dialysis.

Duration of use

The duration of treatment will be individually determined by the doctor and depends on the respective indication (see Dosing).

If you are given more Nadroparin Calcium Aspen than you should

The protraction of the activated Partial Thromboplastin Time (aPTT) value should be considered only as a sign of an overdose in haemodialysis patients and in the treatment of deep vein thrombosis. An increase of the dose with the goal of aPTT protraction carry the risk of overdose or bleeding. Bleeding is the main sign of overdose. Monitoring the platelet count and other coagulation parameters is advisable. Minor bleeding rarely requires specific treatment. It often suffices to reduce or delay the next Nadroparin Calcium Aspen dose. The administration of protamine sulphate should only be considered if the condition of the patient is serious. The anticoagulant effect of Nadroparin Calcium Aspen is widely neutralized, though a certain residual anti-Xa activity will remain (approx. 25%). 6 mg protamine sulphate neutralize about 950 I.U. anti-Xa nadroparin calcium.

If you forget to take Nadroparin Calcium Aspen

If you forget an injection of Nadroparin Calcium Aspen, the daily administration should be immediately continued. Do not inject twice within the same day under any circumstances.

If you stop taking Nadroparin Calcium Aspen

Injections should be taken for the duration indicated by the doctor to guarantee reliable antithrombotic protection. If this is not possible, for example, when side effects develop, please consult with your physician.

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

4. Possible side effects

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

Symptoms you need to look out for

Allergic reactions: These rarely occur when using Nadroparin Calcium Aspen. The signs are:

- Raised skin and itching reddening (hives)
- Swelling, sometimes in face or mouth (angioedema), which cause difficulties when breathing

Skin damage on the injection site

Immediately see a doctor and discontinue the use of Nadroparin Calcium Aspen if you have any of these symptoms.

The information on the frequency of side effects is based on the following categories:

Very common: more than 1 patient in 10
Common: 1 to 10 patients in 100
Uncommon: 1 to 10 patients in 1,000
Rare: 1 to 10 patients in 10,000
Very rare: less than 1 patient in 10,000
Not known (cannot be estimated from the available data)

Side effects

The following side effects have been observed to date. Approx. 3% of treated patients developed adverse effects.

Very common:

- Blood clotting (minor hematoma) on the injection site, in some cases with nodules (granulomas)
- Bleeding at different spots

Common:

- Irritation on the injection site
- Open or latent complications of bleeding (especially on the skin, mucosa, wounds as well as in the gastrointestinal and genitourinary tract) which may result in anaemia (haemorrhagic anaemia)
- Elevated liver parameters (transaminases, gamma-GT), LDH, and Lipase
- Elevated serum potassium levels

Uncommon:

- Minor, transient platelet count (type I thrombocytopenia) (see Section 2. Warnings and precautions)

Rare:

- Calcium deposits on the injection sites (calcinosis), especially in patients with severe renal impairment
- Allergic reaction with symptoms such as nausea, vomiting, elevated temperature, headaches, hives (urticaria), itching (pruritus), shortness of breath (dyspnoea), spasm of the upper airways (bronchospasm), drop in blood pressure

- Transient aldosterone deficiency (hypoaldosteronism)
- Severe, heparin-related drop in the platelet count (type II thrombocytopenia) (see Section 2. Warnings and precautions)
- Increase in platelet count (thrombocytosis)
- Increase in white blood cell count (eosinophilia)
- Anaphylactic reaction, anaphylactic shock, angioedema
- Skin rash, skin reddening (erythema)
- Hair loss (alopecia)
- Skin damage (skin necrosis) on the injection site (see Section 2. Warnings and precautions)

Very rare:

- Elevated platelet count (thrombocythemia over 1,000,000/mm³, primarily observed after surgery)
- Hypersensitivity reactions (including skin reactions)
- Persistent painful penile erection (priapism)
- Tissue damage at the injection site (necrosis)

Not known:

- Headache
- Migraine

Cases of severe adverse drug reactions such as intracranial bleeding and bleeding of the eyes were reported. Peridural bleeding in the lumbar region after spinal anaesthesia resulting in paraplegia were observed.

Bleeding

Bleeding is the main sign of overdose. Please immediately notify your doctor, if you develop problems/complications with bleeding.

Minor bleeding rarely requires specific treatment. It often suffices to reduce or delay the next Nadroparin Calcium Aspen dose.

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:

[To be completed nationally]

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

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

Do not use this medicine after the expiry date which is located on the outer carton and on the pre-filled syringe. The expiry date refers to the last day of that month.

Nadroparin Calcium Aspen must not be mixed with other preparations.

Do not use Nadroparin Calcium Aspen, if you notice the following:
Opacity or discoloration of the solution.

Only use clear solutions for injection. For single use only. Any unused residual solution should be discarded.

Do not store above 30 °C.

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

6. Contents of the pack and other information

What Nadroparin Calcium Aspen contains

- The active substance is:
Nadroparin calcium

A pre-filled syringe of Nadroparin Calcium Aspen with 0.4 ml solution for injection contains 3,800 I.U. anti-Xa Nadroparin-Calcium (equal to 95 to 130 I.U. anti-Xa/mg).

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

What Nadroparin Calcium Aspen looks like and contents of the pack

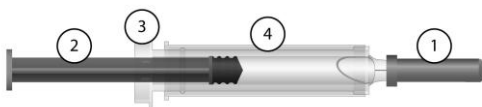
The Nadroparin Calcium Aspen pre-filled syringe contains a clear to slightly opalescent, colourless or light yellow, light brown or slightly dark yellow solution. The cylinder-shaped barrel is made of glass. The needle is made of stainless steel and is protected by a protective cap which can contain natural rubber (Latex). The movable piston is made of orange plastic.

Nadroparin Calcium Aspen is available as a pack with 2 pre-filled syringes, with 10 pre-filled syringes, with 20 pre-filled syringes and as a hospital pack with 100 pre-filled syringes each with 0.4 ml solution for injection. Not all pack sizes may be marketed.

Step by step instruction:

Parts of the Fraxiparine pre-filled syringe:

- ① Tip cap
- ② Piston
- ③ Finger flange
- ④ Barrel



Information on use

1. Wash your hands carefully with warm soap and water and dry them with a towel.

2. Remove the syringe from the carton and inspect it:

- Check the expiration date located on the outer carton and on the pre-filled syringe.
- check whether the syringe has been opened or damaged

3. Sit or lie down in a comfortable position

Select a section of skin in the lower abdominal region, at least 5cm under the navel (Fig. A).

Switch from left to right when choosing an injection site in the lower abdominal region for each injection. This helps to prevent tissue damage at the injection site. If it is not possible to inject in the lower abdominal region, consult your doctor.

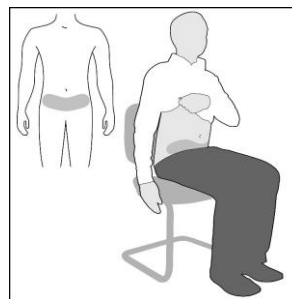


Fig. A

4. Wipe the injection site with an alcohol pad.

5. Remove the tip cap by first turning and then pulling it up in a straight line away from the syringe (Fig. B).

Discard the tip cap.

- Place the syringe upright so that the needle is facing down.
- Press the plunger carefully down until the bottom side of the air bubble is located on the marking with the volume that the doctor prescribed.
- Allow the liquid to drip from the needle onto a cloth and wipe this back.
- The syringe is now ready for use.

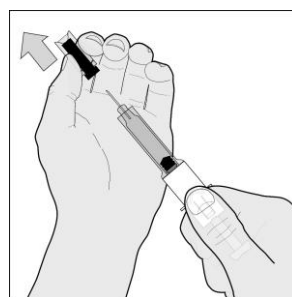


Fig. B

Important information:

- Do not touch anything with the needle and do not touch the needle itself.
- It is normal if you see an air bubble in the pre-filled injection. **Try not to remove the air bubble before you perform the injection** - otherwise a part of the medicinal product can be lost.

6. Press the cleansed area of skin so that a skin fold forms.

Hold the skin fold during the entire injection process between the thumb and the index finger (Fig. C).

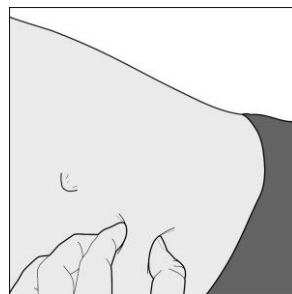


Fig. C

7. Hold the pre-filled syringe firmly at the finger flange. Inject the complete length of the needle at a right angle into the skin fold (Fig. D).

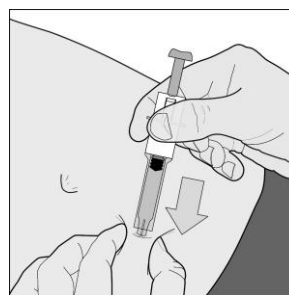


Fig. D

8. Inject the ENTIRE content of the pre-filled syringe under the skin by pressing the plunger until it reaches the bottom of the barrel (Fig. E). Afterwards remove the needle carefully from the skin.

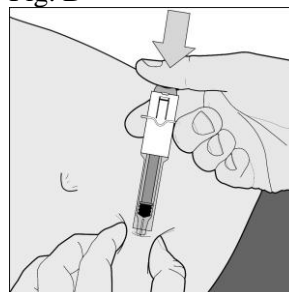


Fig. E.

9. After use hold the pre-filled syringe with one hand at the safety barrel. Pull the finger flange back with the other hand. This unlocks the barrel. Push the barrel over the syringe until it locks over the needle (Fig. F).

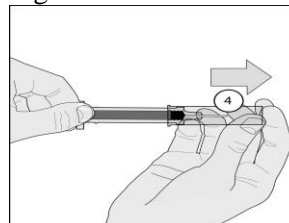


Fig. F

Marketing Authorisation Holder and manufacturer

Marketing Authorisation Holder:

Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland
Phone: [To be completed nationally]

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:

Italy, Portugal, Spain: Fraxiparina

Belgium, Bulgaria, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hungary, Latvia, Liechtenstein, Lithuania, Luxembourg, Netherlands, Poland, Republic of Cyprus, Romania, Slovakia,

Slovenia: Fraxiparine

Germany: Fraxiparine Duo

Austria: Fraxiparin-Fertigspritze

This package leaflet was last approved in <Month Year>