Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nadroparin Calcium Aspen 5,700 I.U. anti-Xa/ 0.6 ml solution for injection in a pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 9,500 I.U. anti-Xa Nadroparin-Calcium derived from porcine intestinal mucosa, equal to 95 to 130 I.U.
anti-Xa/mg, a low molecular weight heparin with a mean molecular weight of 4,500 Dalton.

1 Pre-filled syringe with 0.6 ml solution for injection contains 5,700 I.U. anti-Xa Nadroparin-Calcium.

For the full list of the excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
The solution is sterile and clear, pH 5.0 to 7.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Posology

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) subcutaneously 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 orthopedic 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 orthopedic 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 should be subcutaneously injected twice daily (every 12 hours), usually for a duration of 10 days, s.c. injected and at a dose adapted to the patient's body weight (see following table). The administration of oral anticoagulants should be started from day 1. The duration of the treatment with nadroparin is at least 5 days and should be continued until sufficient oral anticoagulation has been achieved.

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 pre-filled syringes are filled to 0.6 ml, 0.8 ml and 1.0 ml graduated in 0.1 ml units. For patients 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.

Anticoagulation during hemodialysis and hemofiltration

The dose must be individually adapted to each patient. Nadroparin 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 hemodialysis and hemofiltration intra-arterial injection at the beginning of dialysis
< 50	0.3 ml
50 to 69	0.4 ml
≥ 70	0.6 ml

Monitoring during treatment
The platelet count must be checked at regular intervals during treatment with Nadroparin 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/µl and 150,000/µl. 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/µl 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 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.

Paediatric population
Nadroparin is not recommended for children and adolescents, since there are insufficient data on safety and efficacy to determine the dose for patients under the age of 18 years.

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 before starting therapy (see *Renal impairment* below and under Section 5.2).

Hepatic Impairment
No studies were conducted in patients with hepatic impairment.

Renal impairment
Moderate to severe impairment of the kidney function is associated with increased exposure to nadroparin. These patients are subject to an increased risk of thromboembolism and hemorrhage.

- *Treatment of deep vein thrombosis*

If patients with renal failure (see Section 4.3) 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.

- *Prophylaxis of thromboembolic disorders*

A dose reduction is not necessary in patients with minor impairment of the kidney function (creatinine clearance ≥ 50 ml/min.).

If in light of the individual risk factors for hemorrhage and thromboembolism a dose reduction for patients with moderate impairment of the kidney function (creatinine clearance ≥ 30 ml/min. and < 50 ml/min.) is deemed adequate by the prescribing physician, the dose should be reduced by 25% to 33% (see Sections 4.4 and 5.2).

Nadroparin is contraindicated in patients with severe impairment of the kidney function (creatinine clearance below 30 ml/min) (see Section 4.3).

Method of administration
Nadroparin is not intended for intramuscular injection.

The lateral abdominal wall is the usual injection site for the subcutaneous application of nadroparin; alternatively, nadroparin 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 is injected into the femoral artery during dialysis.

4.3 Contraindications

Nadroparin should not be used in patients with:
- Hypersensitivity to the active substance, heparin, or to any of the excipients listed in section 6.1.
- Current or history of heparin-associated thrombocytopenia (type II) or history of nadroparin-associated thrombocytopenia (see Section 4.4)
- Intraocular bleeding or other active bleeding processes or increased risk of bleeding due to a haemostatic disorder (haemorrhagic diathesis, coagulation factor deficiency, severe thrombocytopenia), except with disseminated intravascular coagulation which is not induced by heparin
- Organ lesions susceptible to bleeding such as acute gastrointestinal ulcers, cerebral bleeding, and cerebral aneurysm
- Haemorrhagic stroke
- Acute infectious endocarditis
- Severe, uncontrollable hypertension
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance < 30 ml/min.) except in case of haemodialysis treatment
- Injuries and surgical procedures of the central nervous system as well as on eye and ear
- Retinopathy, vitreous body haemorrhage
- Imminent miscarriage
- Treatment of deep vein thrombosis: Regional anaesthesia (spinal or epidural anaesthesia), lumbar puncture

4.4 Special warnings and precautions for use

Thrombocytopenia and platelet function disorders.

Heparin-induced thrombocytopenia
Due to the possibility of a heparin-induced thrombocytopenia the **platelet count should be checked throughout the entire nadroparin treatment**.

Heparin-induced thrombocytopenia with occasionally severe course was reported in rare cases which may be associated with arterial or venous thrombosis. Such a diagnosis should be considered in the following situations:

- Thrombocytopenia
- Any significant reduction in the platelet count (30% to 50% of the initial value)
- Deterioration of the initial thrombosis in the course of the therapy
- Thrombosis occurring in the course of the therapy
- Disseminated intravascular coagulation

In this case, the nadroparin treatment must be discontinued.

These effects are probably of an autoimmune/allergic nature and are mainly reported between day 5 and day 21 of the treatment in the case of a first therapy. However, they may occur significantly earlier, if the patient has a history of heparin-induced thrombocytopenia.

If the patient has a history of thrombocytopenia with heparin (either standard or low molecular weight heparin), treatment with nadroparin can be considered, if necessary. Careful clinical monitoring and the check of the platelet count is necessary at least daily in such cases. If thrombocytopenia develops, treatment should be immediately discontinued.

If thrombocytopenia develops with heparin (either standard heparin or low molecular weight heparin), substitution with a different class of antithrombotics should be considered. If unavailable, substitution with a different low molecular weight heparin can be considered, if the use of heparin is indispensable. In such cases the platelet count should be checked at least daily and the treatment should be discontinued as soon as possible, since cases of initial

thrombocytopenia were reported which persisted after substitution (see Section 4.3).

In vitro platelet aggregation tests are only of limited value in the diagnosis of heparin-induced thrombocytopenia.

Special care should be taken, if nadroparin is used in the following situations, since they may be associated with an increased risk of bleeding:

- Liver failure
- Severe arterial hypertension
- History of peptic ulcers, suspected intracranial tumors with susceptibility to bleeding or other organic lesions which are susceptible to bleeding
- Vascular disorders of the retinal membrane
- During the postoperative phase after surgery of the brain, spinal cord or eye
- Simultaneous treatment with oral anticoagulants

Special care must be taken when using nadroparin in patients with hepatic or pancreatic disorders, kidney and/or ureteral stones, in patients who take medicinal products which increase the serum potassium level, and patients who recently had surgery and receive high-dose treatment with nadroparin.

Hyperkalaemia
Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients with raised plasma potassium, or at risk of increased plasma potassium levels, such as patients with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis or those taking drugs that may cause hyperkalaemia (e.g. angiotensin-converting (ACE) inhibitors, Nonsteroidal anti-inflammatory drugs [NSAIDs]).
The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible.
Plasma potassium should be monitored in patients at risk.

Spinal or epidural anesthesia/lumbar puncture and the accompanying administration of medicinal products
Lumbar puncture, spinal or epidural anesthesia are contraindicated in patients who receive curative treatment with nadroparin due to the risk of hematoma formation which can cause persistent neurological deficits and paraplegia (see Section 4.3). Nadroparin should be used only with caution and after careful risk/benefit assessment in patients who receive preventive treatment and have a lumbar puncture, spinal or epidural anesthesia. The risk of a spinal/epidural hematoma is increased by an epidural indwelling catheter or by the simultaneous administration of other medicinal products which also influence blood clotting such as NSAIDs, platelet aggregation inhibitors or other anticoagulants. The risk also seems to increase by traumatic or repeated epidural or spinal punctures. To date no results from randomized, controlled clinical studies are available which prove the safe use of higher doses of nadroparin (for example, for deep vein thrombosis prophylaxis in patients with high thromboembolic risk) with the simultaneous use of anesthetic methods applied close to the spinal cord.

For this reason neuraxial blockade and therapy with anticoagulants should be prescribed only after careful individual risk/benefit assessment:

- The benefit of neuraxial blockade must be carefully weighed against the risks in patients who receive treatment with anticoagulants.

- The benefit of an anticoagulant therapy must be carefully weighed against the risk in patients where an elective surgery with neuraxial blockade is planned.

At least 12 hours should pass between the nadroparin injection at a prophylactic dose, or 24 hours if a therapeutic dose was administered, and the insertion or removal of the spinal/epidural catheter or needle in the case of patients with lumbar puncture, spinal or epidural anesthesia, whereby the product characteristics and the patient profile need to be taken into consideration. Longer intervals can be considered for patients with renal impairment. The following doses should be administered after at least four hours. The additional administration of nadroparin should be delayed until the surgical procedure has been concluded.

The patients should undergo frequent checks with regard to signs and symptoms of neurological deficits such as back

pain, sensory and motor deficits (numbness and weakness of the lower limbs), disturbances of rectal and/or bladder functions. If a neurological disorder is determined, treatment should be started immediately. The medical staff should be trained to detect such signs and symptoms. The patients should be instructed to immediately notify their physician, if they experience one of these symptoms.

If signs or symptoms of spinal hematoma are suspected, diagnostics and treatment should be initiated as soon as possible including a spinal cord decompression.

If significant or obvious bleeding occurs while placing a catheter, careful risk/benefit assessment should be performed before starting or continuing the heparin therapy.

Salicylates, nonsteroidal anti-inflammatory drugs, and platelet aggregation inhibitors
In the prophylaxis or treatment of venous thromboembolic disorders and in the prevention of clotting during haemodialysis, the concomitant use of aspirin, other salicylates, NSAIDs, and anti-platelet agents is not recommended, as they may increase the risk of bleeding. Where such combinations cannot be avoided, careful clinical and biological monitoring should be undertaken.

Special Patient Populations

Paediatric population
No clinical experience is available for the use of nadroparin in children. For this reason the use of nadroparin in children is not recommended until additional data becomes available.

Elderly patients
It is recommended to check the kidney function before starting treatment (see Section 4.3).

Renal impairment
Nadroparin is mainly excreted via the kidney which leads to an increased nadroparin exposure of patients with renal impairment (see Section 5.2). Patients with renal impairment should be treated with care, since they have an increased risk of bleeding.

A reduced dose can be considered for patients with minor to moderate renal failure (creatinine clearance ≥ 30 ml/min. and < 60 ml/min.) who receive curative treatment (see Section 4.2). The decision whether a dose reduction is appropriate for a patient who receives prophylactic therapy and has a creatinine clearance of ≥ 30 and < 50 ml/min. should be made on the basis of the medical evaluation of the individual patient risk for bleeding versus the risk of thromboembolism (see Section 4.2).

Skin necrosis
Skin necrosis was observed in very rare cases under standard or low molecular weight heparin, usually on the injection side, which is proceeded by purpura or infiltrated or painful erythematous skin with or without generalized symptoms. In these cases treatment should be immediately discontinued.

Method of administration
Nadroparin must not be administered through intramuscular or intravenous injection.

The intramuscular injection of other medicinal products should be avoided during therapy with nadroparin due to the risk of developing hematomas.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants, system (gluco-) corticosteroids, and dextran
Nadroparin should be used with care in patients who receive oral anticoagulants, system (gluco-) corticosteroids, and dextran.

The administration of nadroparin 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.

Salicylates, nonsteroidal anti-inflammatory drugs, and platelet aggregation inhibitors
The simultaneous use of acetylsalicylic acid (or other salicylates), nonsteroidal anti-inflammatory drugs, and platelet aggregation inhibitors is not recommended, since these can increase the risk of bleeding (see Section 4.4).

Nitroglycerin
The interaction of heparin with intravenous nitroglycerin, which can reduce the effect of heparin, cannot be excluded for nadroparin. Medicinal products which increase the serum potassium level must only be used under especially careful medical monitoring during the simultaneous use of nadroparin.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have not shown any teratogenic or foetotoxic effects. However, there is only limited clinical data concerning transplacental passage of nadroparin in pregnant women. Experiences based on a limited number of uses of nadroparin during pregnancy showed no undesirable effects on the pregnancy or the health of the fetus/newborn. Additional epidemiological data are not available. For this reason the use of nadroparin is not recommended during pregnancy unless the therapeutic benefit exceeds the potential risk.

Breast-feeding
There is limited information on the excretion of nadroparin in breast milk. Therefore, the use of nadroparin during breast feeding is not advised.

Fertility
There are no clinical studies available on the effect of nadroparin on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most common adverse effects are hemorrhagic manifestations, minor hematomas on the injection site, open or latent complications of bleeding (especially on the skin, mucosa, wounds and in the region of the gastrointestinal and genitourinary tract), elevated transaminases, reactions on the injection site, increase of serum potassium concentration, and an increase of transaminase, gamma-GT, LDH, and lipase concentrations.

Approx. 3% of treated patients developed adverse effects.

The adverse effects are listed below by MedDRA system organ class and categories of frequency.

The information on the frequency of adverse effects is based on the following categories:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
Blood and lymphatic system disorders	Hemorrhagic manifestations at different sites (including cases of spinal	Open or latent complications of bleeding (especially on the skin, mucosa,	Minor, transient thrombocytopenia	Thrombocytopenia (including antibody-induced heparin-induced thrombocytopenia (type II) see Section 4.4)	Thrombocythemia over 1,000,000/mm^3, mainly postoperative observation	

	hematoma), more frequent in patients with other risk factors (see Sections 4.3 and 4.4)	wounds, and in the region of the gastrointestinal and genitourinary tract) which may cause hemorrhagic anemia		Thrombocytosis Eosinophilia which is reversible after discontinuation		
Immune system disorders				Anaphylactic shock, anaphylactic reactions, angioedema	Hypersensitivity reactions (including skin reactions)	
Nervous system disorders						Headache Migraine
Endocrine disorders				Reversible hyperkalaemia		
Metabolism and nutrition disorders					Reversible hyperkalaemia in the context of heparin-induced aldosterone suppression, especially in risk patients (see Section 4.4)	
Hepatobiliary disorders		Elevated transaminases, normally transient				
Reproductive system and breast disorders					Priapism	
Skin and subcutaneous tissue disorders				Skin rash, urticaria, erythema, pruritus Alopecia Skin necrosis, normally on the injection site (see Section 4.4)		
General disorders and administration site conditions	Minor hematoma on the injection site In some cases the development of solid nodules can be noticed which does not indicate the encapsulation of heparin. These nodules usually disappear after a few days.	Reactions on the injection site		Calcinosis on the injection site Calcinosis more commonly occurs in patients with a pathological calcium/phosphate product as occurs in some cases of chronic renal failure Allergic reactions with symptoms such as nausea, vomiting, elevated temperature, headaches, urticaria, pruritus, dyspnea, bronchospasm, hypotension		
Investigations		Elevated serum potassium concentration Elevated transaminase, gamma-GT, LDH, and lipase concentrations				

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms and Signs
The protraction of the activated Partial Thromboplastin Time (aPTT) value should be considered only as the extent of the overdose in hemodialysis patients and in the acute therapy 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.

Treatment
Minor bleeding rarely requires specific treatment. It often suffices to reduce or delay the next nadroparin dose. The administration of protamine sulfate should only be considered if the condition of the patient is serious.
It largely neutralises the anticoagulant effect of nadroparin but some anti-Xa activity will remain.
0.6 ml of protamine sulphate neutralises about 950 I.U. anti-Xa nadroparin. The amount of protamine to be injected, should take into account time elapsed from the injection of heparin, and a dose reduction of protamine may be appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent - Heparin group, ATC code: B01A B06

Nadroparin calcium is the calcium salt of nadroparin, a low molecular weight heparin with a mean molecular weight of about 4,500 Dalton; it is produced by depolymerization of standard heparin. Structurally, this is a glycosaminoglycan. Nadroparin especially inhibits factor Xa and to a lesser extent thrombin. The inhibition is partially mediated by the plasma protease inhibitor antithrombin III. Compared to heparin nadroparin has a lesser effect on platelet function and aggregation and only a minor effect on primary hemostasis. The biological activity of different low molecular weight heparins cannot be expressed with a test which allows for the simple comparison of doses between different preparations.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters were determined through the measurement of anti-Xa activity in the plasma.

Absorption
The maximum anti-Xa activity (c_{max}) is achieved approx. 3 hours (t_{max}) after subcutaneous injection. The maximum anti-Xa concentration in the plasma is reached within less than 10 minutes after intravenous injection, the half-life is approx. 2 hours. The bioavailability with regard to the anti-Xa activity is almost complete (approx. 88 %).

Elimination
The elimination half-life after subcutaneous injection is approx. 3.5 hours.

Special Patient Populations

Renal impairment
A clinical study on the pharmacokinetics of intravenously administered nadroparin in patients with renal impairment of different degrees determined a correlation between the nadroparin clearance and the creatinine clearance.

Compared to health subjects the mean AUC as well as elimination half-life was increased by 52% and 39% respectively in patients with moderate renal impairment (creatinine clearance 36-43 ml/min.). The mean plasma clearance of nadroparin was reduced to 63% of the normal value in these patients. Severe interindividual fluctuations were observed in the study. The mean AUC and elimination half-life in patients with severe renal impairment (creatinine clearance 10-20 ml/min.) was increased by 95% and 112% respectively compared to healthy subjects. The plasma clearance of patients with severe renal impairment was reduced by 50% compared to patients with normal kidney function. The mean AUC and elimination half-life in hemodialysis patients (creatinine clearance 3-6 ml/min.) was increased by 62% and 65% respectively compared to healthy subjects. The plasma clearance of hemodialysis patients was reduced by 67% compared to patients with normal kidney function (see Sections 4.2 and 4.4).

5.3 Preclinical safety data

Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydroxide
or
Hydrochloric acid 10% (for pH adjustment)
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Pre-filled syringe comprised of a Type I glass barrel with stainless steel needle and tip cap made of natural and/or styrene-butadiene rubber, a safety barrel made of polypropylene and a piston with sealing lip made of chlorobutyl elastomer.

Nadroparin calcium Aspen 5,700 I.U. anti-Xa/ 0.6 ml
Pack with 2, 10, 20 and 50 graduated pre-filled syringes each with 0.6 ml solution for injection, Hospital pack with 100 graduated pre-filled syringes each with 0.6 ml solution for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Information on handling:
Perform visual check for particles and discoloration before use. Only use solutions for injection whose appearance has not changed. For single use only. Discard any unused residual solution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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.

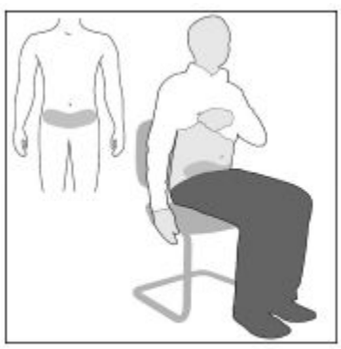

Fig. A

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**).

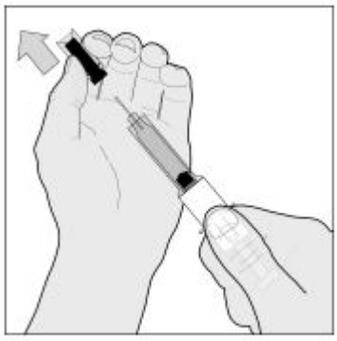

Fig. B

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.

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**).

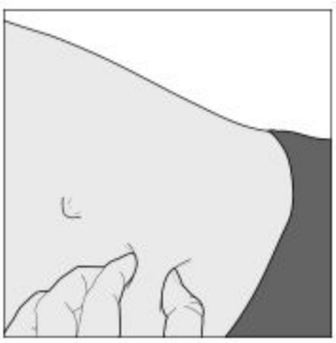

Fig. C

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**).

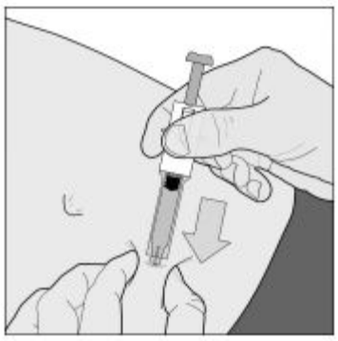

Fig. D

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.

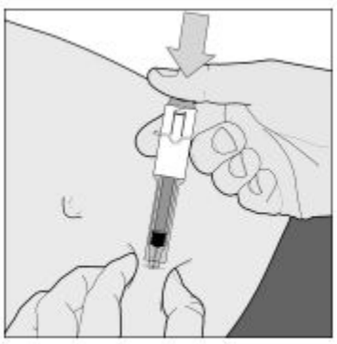

Fig. E.

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**).

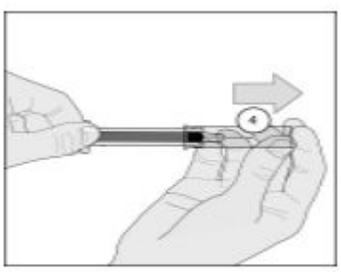

Fig. F

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/020/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th May 2018

10 DATE OF REVISION OF THE TEXT

August 2018