Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nadroparin calcium Aspen Forte 19,000 I.U. anti-Xa/ml solution for injection in a pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1.0 ml solution for injection contains 19,000 I.U. nadroparin calciumderived from porcine intestinal mucosa, equivalent to 95 - 130 I.U. anti-Xa/mg, a low-molecular heparin with a mean molecular weight of 4,500 Daltons.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injectionin pre-filled syringe. The solution is sterile and clear, pH 4.5 to 7.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of deep venous thrombosis.

4.2 Posology and method of administration

Posology

Treatment of deep venous thrombosis.

Nadroparin 19,000 I.U. should be injected subcutaneously once daily for the duration of 10 days in a dosage appropriately adjusted for the patient's body weight (see Table below).

The administration of oral anticoagulants should be started on the first day. The duration of treatment with Nadroparin 19,000 I.U. is at least 5 days and should be continued until sufficient oral anticoagulation has been achieved.

In patients with thrombophilia or complicated deep venous thrombosis, or in patients with increased risk of bleeding complications, a twice-daily administration of nadroparin calcium should be considered (see Fraxiparine).

The prefilled syringes 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

Weight in kg	Treatment of deep venous thrombosis ml subcutaneous injection once 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

Monitoring during treatment
Because of the risk of heparin-induced thrombocytopenia, the platelet count must be monitored regularly during treatment with Nadroparin 19,000 I.U.

Checking the platelet count is recommended prior to initiating treatment, during the first day of treatment and subsequently every 3 to 4 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 19,000 I.U. 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.

Paediatric population
Nadroparin is not recommended in children and adolescents, as there are insufficient data on safety and efficacy to determine dosages for patients younger than 18 years of age.

Elderly patients

Dosage adjustment in elderly patients is not necessary, except in case of kidney disorders. It is recommended to monitor the kidney function in elderly patients prior to starting treatment (see *Impaired renal function* below and under section 5.2).

Patients with impaired hepatic function

There have been no studies conducted in patients with hepatic impairment.

Impaired renal function

Moderate and severe renal impairment is associated with increasing exposure to nadroparin. These patients are at an increased risk of thromboembolism and haemorrhage.

If patients with renal impairment (see section 4.3) 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 the 4th day, 4 to 6 hours following subcutaneous application. Anti-Xa values above 1.8 I.U./ml may be an indication of an overdose and should lead to a dose reduction.

Nadroparin is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min) (*see section 4.3, Contraindications*).

Method of administration
For subcutaneous administration of Nadroparin 19,000 I.U., the lateral abdominal wall is the usual site of injection. As an alternative, Nadroparin 19,000 I.U. can be injected into the thigh.

The needle is inserted perpendicularly into a fold of skin formed between the thumb and index finger that should be gently but firmly held until injection has been completed. The injection site should not be rubbed.

4.3 Contraindications

Nadroparin 19,000 I.U. should not be used in patients with:
- hypersensitivity to the active substance(s), heparin, or to any of the excipients listed in section 6.1.

- history of, or current heparin-associated thrombocytopenia (Type II) or known nadroparin-associated thrombocytopenia (see section 4.4)
- interocular bleeding or other active bleeding processes or increased risk of bleeding related to haemostasis disorders (haemorrhagic diathesis, coagulation factor deficiency, severe thrombocytopenia), except for disseminated intravascular coagulation that is not induced by heparin
- organ lesions that may have a tendency to bleed such as acute gastro-intestinal ulcers, cerebral haemorrhage and cerebral aneurysm
-haemorrhagic stroke
-acute infective endocarditis
- severe, unmanageable high blood pressure
- severe hepatic impairment
- severe renal impairment (creatinine clearance < 30 ml/min)
- injuries of and surgical procedures on the central nervous system as well as the eyes and ears
- retinopathies, vitreous haemorrhage
- miscarriage
- regional anaesthesia (spinal or epidural anaesthesia)
- lumbar puncture

4.4 Special warnings and precautions for use

Thrombocytopenia and platelet function disorders

Heparin-induced thrombocytopenia
Because of the possibility of heparin-induced thrombocytopenia, **the platelet count should be monitored throughout the course of treatment with nadroparin**.

Rare cases of heparin-induced thrombocytopenia that occasionally became severe have been reported, which may be associated with arterial or venous thrombosis. Such diagnosis should be considered in the following situations:

- thrombocytopenia
- any significant reduction in platelet count (30 to 50% compared with the baseline value).
- worsening of the initial thrombosis during the course of treatment
- thrombosis occurring during the course of treatment
- disseminated intravascular coagulation

In this event, nadroparin treatment must be discontinued.

These effects are probably of an immuno-allergic nature and, in the case of a first treatment, are reported mainly between the 5th and the 21st day of treatment. They may also occur much earlier if there is a history of heparin-induced thrombocytopenia.

If there is a history of thrombocytopenia with heparin (either standard or low-molecular weight heparin), treatment with nadroparin may be considered, if necessary. In such cases, careful clinical monitoring and platelet count measurement should be performed at least daily. If thrombocytopenia occurs, treatment must be discontinued immediately.

When thrombocytopenia occurs with heparin (either standard or low-molecular weight heparin), substitution with a different class of antithrombotic drugs should be considered. If not available, substitution with another low-molecular weight heparin may be considered if administration of heparin is inevitable. In such cases, platelet count measurement should be performed at least daily and treatment should be discontinued as soon as possible, as cases of initial thrombocytopenia that have continued after substitution have been described (see section 4.3).

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

Caution should be exercised when nadroparin is administered in the following situations, as they may be associated with an increased risk of bleeding:

-hepatic insufficiency
-severe arterial hypertension
-history of peptic ulceration, suspicion of intracranial tumours likely to bleed or other organic lesions that are likely to bleed

-chorioretinal vascular disease
-during post-operative period following brain surgery, spinal cord surgery or eye surgery
-concomitant treatment with oral anticoagulants

Nadroparin 19,000 I.U. should be used with caution in patients with impaired liver or pancreatic function, in patients with kidney and/or ureteral stones, in patients who are taking medicines that increase the plasma potassium concentration, as well as in patients who recently underwent surgery and are receiving a high-dosage treatment with Nadroparin 19,000 I.U.

The use of Nadroparin 19,000 I.U. is not recommended in patients who underwent surgery within the last 5 days.

Hyperkalaemia
Heparin may suppress adrenal secretion of aldosterone, which can lead to hyperkalaemia particularly in patients with elevated plasma potassium concentrations or in patients at risk for elevated plasma potassium 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 [angiotensin-converting enzyme], 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.

Spinal or epidural anaesthesia/lumbar puncture and concomitant drugs
Because of an increased risk of hematoma formation, which may lead to persistent neurological deficits and paraplegia, lumbar puncture, spinal or epidural anaesthesia is contraindicated in patients who receive a curative treatment with Nadroparin 19,000 I.U. (see section 4.3). Nadroparin 19,000 I.U. should be used with caution and after careful individual risk/benefit assessment in patients who receive preventive treatment and who receive a lumbar puncture, or spinal or epidural anaesthesia. The risk of a spinal/epidural hematoma is increased by in-dwelling epidural catheters or by the concomitant use of other drugs, which also affect haemostasis, such as NSAIDs, platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture. So far, no results from randomized, controlled clinical studies are available that substantiate the safe use of higher doses of Nadroparin 19,000 I.U. (for instance for the prophylaxis of deep venous thrombosis in patients with high thromboembolic risk) with concomitant administration of regional spinal anaesthesia. Therefore, the concomitant prescription of a neuraxial blockade and treatment with anticoagulants should be decided on after careful individual benefit-risk assessment in the following situations:

-In patients who are already treated with anticoagulants, the benefits of a neuraxial blockade must be carefully weighed against the risks.

-In patients planned to undergo elective surgery with neuraxial blockade, the benefits of anticoagulant treatment must be carefully weighed against the risks.

In the case of patients with spinal lumbar puncture, spinal anaesthesia or epidural anaesthesia, a minimum of 12 hours should elapse between the nadroparin injection at prophylactic doses or 24 hours at treatment doses and the insertion or the removal of the spinal/epidural catheter or needle, whereby the product characteristics and the patient profile must be taken into account. For patients with renal impairment, longer intervals may be considered. Subsequent doses should only be given if at least four hours have passed. New administration of nadroparin should be postponed until the surgery is completed.

Patients should be frequently monitored for signs and symptoms of neurological impairment, such as backaches, sensory and motor deficits (numbness and weakness in the lower limbs), intestinal and/or bladder dysfunction. If neurological impairment is determined, urgent treatment should begin immediately. Nursing personnel should be trained to detect such signs and symptoms. Patients should be instructed to call their doctor immediately if they perceive any of these symptoms.

If signs and symptoms of spinal hematoma are suspected, an immediate diagnosis and treatment, including spinal cord decompression**,** should be initiated.

If, during placement of the catheter, significant or obvious bleeding occurs, a careful benefit-risk assessment should take place before starting or continuing heparin treatment.

Salicylates, non-steroidal anti-inflammatory and anti-platelet drugs

The concomitant use of acetylsalicylic acid, other salicylates, non-steroidal anti-inflammatory and anti-platelet drugs is not recommended, as they may increase the risk of bleeding. Where such combinations cannot be avoided, careful clinical and biological monitoring should be performed.

Special Patient Populations

Paediatric population
No adequate clinical data for use of Nadroparin 19,000 I.U. in children is presently available.
The use of Nadroparin 19,000 I.U. in children is therefore not recommended until more data are available.

Elderly patients
It is recommended to monitor the renal function prior to starting treatment (see section 4.3).

Impaired renal function
Nadroparin is primarily excreted via the kidneys, which leads to elevated nadroparin exposure in patients with renal impairment (see section 5.2). Patients with impaired renal function should be treated with caution, as they are at increased risk of bleeding.

For patients with mild to moderate renal insufficiency (creatinine clearance 30 ml/min and <60 ml/min), who are receiving a curative treatment, a reduced dose may be taken into consideration (see section 4.2).

Skin necrosis
In very rare cases, cutaneous necrosis has been observed, typically at the injection site under treatment with standard or low-molecular weight heparin, that was preceded by purpura or infiltrated or painful erythematous skin, with or without general symptoms. In such cases, treatment should be discontinued immediately.

Method of administration
Nadroparin 19,000 I.U. must not be injected intramuscularly or intravenously.

Due to risk of bruising during Nadroparin 19,000 I.U. treatment, intramuscular injection of other medications should be avoided.

4.5 Interaction with other medicinal products and other forms of interactions

Oral anticoagulants, system (gluco-) corticosteroids, and dextran
Nadroparin should be administered with caution in patients who receive oral anticoagulants, systemic (gluco-) corticosteroids and dextrans.

Administration of Nadroparin 19,000 I.U. 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.

Salicylates, nonsteroidal anti-inflammatory drugs, and platelet aggregation inhibitors
The concomitant use of acetylsalicylic acid (or other salicylates), non-steroidal anti-inflammatory and anti-platelet drugs is not recommended, as they may increase the risk of bleeding (see section 4.4).

Nitroglycerin
The interaction of heparin with intravenous nitroglycerin that can lead to a reduced efficacy of heparin also cannot be ruled out for Nadroparin 19,000 I.U. Medicines that increase blood potassium concentrations may only be used concomitantly with Nadroparin 19,000 I.U. under very close medical supervision.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studieshave not shown any teratogenic or fetotoxic effects. However, there is only limited clinical data concerning transplacental passage of nadroparin. Experiences based on a limited number of applications of nadroparin calcium during pregnancy have shown no adverse effects on the pregnancy or the health of the foetus/new-born. Further epidemiological data are not available. Therefore, the use of nadroparin during pregnancy is not advised, unless the therapeutic benefits outweigh the possible risks.

Breastfeeding
There is insufficient information on the excretion of nadroparin calcium in breast milk. Therefore, the use of Nadroparin 19,000 I.U. during breast-feeding is not recommended.

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

4.7 Effects on ability to drive and use machines

There are no data on the effects on the ability to drive and use machines.

4.8 Undesirable effects

The most common adverse effects include haemorrhagic manifestations, minor hematomas at the injection site, open or hidden bleeding complications (particularly affecting the skin, mucous membranes, lesions, as well as the gastrointestinal tract region), elevated transaminase concentration, irritations at the injection site, elevated serum calcium concentrations and elevated aminotransferase, gamma-GT and lipase concentrations.

Adverse reactions are listed below by system organ class and frequency:

The following conventions have been used for the classification of adverse reactions in terms of frequency:

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)

Clinical investigations comparing Nadroparin 19,000 I.U. with the conventional twice-daily administration of nadroparin calcium confirmed the established safety profile of the drug. In this study, 3.8% of the patients treated once daily with nadroparin calcium and 4.5% of the patients treated twice daily with nadroparin calcium experienced adverse effects.

Application experience with nadroparin calcium shows that about 3% of the prophylactically treated patients had adverse reactions.

System organ class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very rare*
Blood and lymphatic system disorders	Haemorrhagic manifestations on various sites (including cases of spinal hematomas), more frequent in patients with other risk factors (see sections 4.3 and 4.4)	Open or hidden bleeding complications (particularly affecting the skin, mucous membranes, lesions, as well as the gastrointestinal tract and urogenital tract regions) that can lead to haemorrhagic anaemia	Mild transient thrombocytopenia (Type I)	Thrombocytopenia (including antibody-mediated heparin-induced thrombocytopenia (Type II) see section 4.4), thrombocytosis, Eosinophilia, which is reversible after discontinuation	Thrombocytopenia above 1,000,000/mm^3, primarily observed postoperatively
Immune system disorders				Anaphylactic shock, anaphylactoid reactions, angioedema	Hypersensitivity reactions (including cutaneous reactions)

System organ class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very rare*
Endocrine disorders				Reversible hyperkalaemia	
Metabolism and nutrition disorders					Reversible hyperkalaemia in conjunction with heparin-induced aldosterone suppression, particularly in patients at risk (see section 4.4)
Hepatobiliary disorders		Elevated transaminases, usually transient			
Reproductive system and breast disorders					Priapism
Skin and subcutaneous tissue disorders				Rash, urticaria, erythema, pruritus alopecia Skin necrosis, usually at the injection site (see section 4.4)	
General disorders and administration site disorders	Minor hematomas at the injection site In some cases, the occurrence of firm nodules, which do not indicate an encapsulation of heparin, may be observed. These nodules usually disappear after a few days.	Reactions at the injection site.		Calcinosis at the injection site Calcinosis occurs more frequently in patients with abnormal calcium phosphate product, such as in some cases of chronic renal insufficiency. Allergic reactions with symptoms such as nausea, vomiting, elevated body temperature, headache, urticaria, pruritis, dyspnoea, bronchospasm, hypotension	
Investigations		Increases in serum potassium concentration Elevated aminotransferase, gamma-GT, LDH and lipase levels			

Cases of serious adverse effects, such as intracranial bleeding and ocular bleeding have also been reported.
Epidural bleeding in the lumbar region following catheterized spinal anaesthesia that can lead to paraplegia has been 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
In the treatment of deep venous thrombosis, prolongation of the activated Partial Thromboplastin Time (aPTT) value should only be considered as an indication ofoverdose. Dose-escalations aiming at aPTT prolongation bear the risk of an overdose or bleeding. Haemorrhage is the major sign of overdose. Monitoring of platelet count and other coagulation parameters is advised.

Treatment
Minor bleeding rarely requires specific treatment. It often suffices to reduce or delay the next nadroparin dose. The administration of protamine sulphate 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, ATC-Code: B01A B06

Nadroparin 19,000 I.U. is the calcium salt of nadroparin, a low-molecular weight heparin with a mean molecular weight of about 4,500 Daltons. It is made by depolymerisation of standard heparin. Structurally it is referred to as a glycosaminoglycan. Nadroparin inhibits Factor Xa in particular and thrombin to a lesser extent. Inhibition is partially mediated via the plasma protease inhibitor antithrombin III. Nadroparin has less effect on platelet function and aggregation and only has a minor effect on primary haemostasis compared to heparin. The biological activity of different low-molecular weight heparins cannot be expressed in a single test that allows simple dose comparison between different preparations.

5.2 Pharmacokinetic properties

The pharmacokinetic properties have been determined by measuring the anti-Xa activity in plasma.

Absorption
Following subcutaneous injection, the maximum anti-Xa activity (C^{max}) was reached after approximately 4 to 6 hours (t^{max}). Following intravenous injection, the maximum anti-Xa concentration in plasma is reached within less than 10 minutes, the half-life is about 2 hours. The bioavailability in terms of anti-Xa activity is nearly complete (about 98%).

Elimination
The elimination half-life following subcutaneous injection is about 8 to10 hours.

Special Patient Populations

Renal Impairment
In a clinical study on the pharmacokinetics of intravenously administered nadroparin in patients with varying degrees of renal impairment, a correlation was found between nadroparin clearance and creatinine clearance. In patients with moderate renal impairment (creatinine clearance 36 – 43 ml/min), the mean AUC as well as the elimination half-life were increased by 52 and 39% respectively, compared to healthy study participants. In these patients, the mean plasma clearance of nadroparin was decreased to 63% of the normal value. In the study, wide inter-individual variability was observed. In patients with severe renal impairment (creatinine clearance 10 – 20 ml/min), the mean AUC and the elimination half-life were increased by 95% and 112% respectively, compared to healthy study participants. The plasma clearance of patients with severe renal impairment was reduced by 50%, compared to patients with normal kidney function. In patients with severe renal impairment (creatinine clearance 10 – 20 ml/min), the mean AUC and the elimination half-life were increased by 62% and 65% respectively, compared to healthy study participants. The plasma clearance of haemodialysis patients with severe renal impairment 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

Store below 25°C.

6.5 Nature and contents of container

The prefilled syringe consists of a Type-I glass cylinder with stainless steel needle and needle guard made of natural and/or styrene-butadiene-rubber, a safety cylinder made of polypropylene and a piston with sealing lip made of butyl elastomer.

Packs with 2, 6 and 10, graduated prefilled syringes, each containing 1.0 ml injection solution (1.0 ml injection solution contains 19,000 I.U. anti-Xa nadroparin calcium).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Prior to administration, visually inspect for particulate matter and discoloration. Discard the injection solution if any visual change has occurred. For single use only. Discard any unused solution.

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

Step by step guide:
Parts of the NADROPARINE CALCIUM 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**).

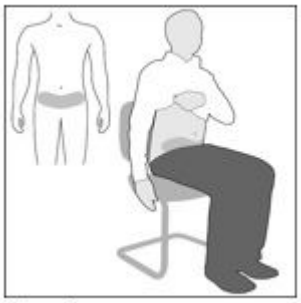
Fig. A

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.

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**).

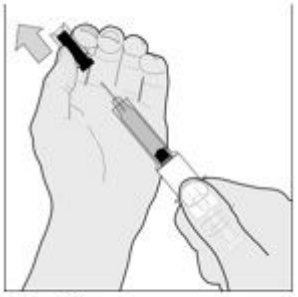
Fig. B

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**.)

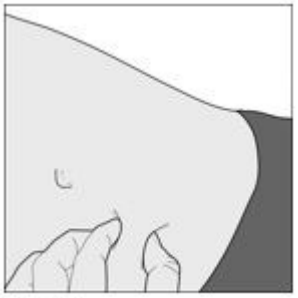

Fig. C

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**).

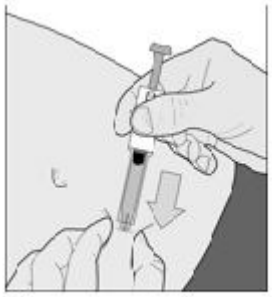

Fig. D

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

Fig. E.

Remove the syringe gently from the skin.

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**).

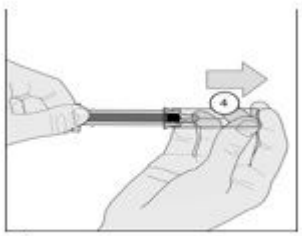

Fig. F

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
Unit 35/36
Grange Parade

Baldoyle Industrial Estate
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2010/065/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th May 2018

10 DATE OF REVISION OF THE TEXT

February 2021