SUMMARY OF PRODUCT CHARACTERISTICS

FRAXIPARINE™/FRAXIPARINE FORTE™/FRAXODI™

Nadroparin

QUALITATIVE AND QUANTITATIVE COMPOSITION

***FRAXIPARINE*™ [Nadroparin calcium solution for injection (9,500 anti-Xa IUPh.Eur./ml)]**

Pre-filled syringes:

- 0.2 ml of solution equivalent to 1,900 anti-Xa IU
- 0.3 ml of solution equivalent to 2,850 anti-Xa IU
- 0.4 ml of solution equivalent to 3,800 anti-Xa IU.

Graduated pre-filled syringes:

- 0.6 ml of solution equivalent to 5,700 anti-Xa IU
- 0.8 ml of solution equivalent to 7,600 anti-Xa IU
- 1 ml of solution equivalent to 9,500 anti-Xa IU.

Multi Dose Vials:

- 2 ml of solution equivalent to 19,000 anti-Xa IU
- 5 ml of solution equivalent to 47,500 anti-Xa IU
- 15 ml of solution equivalent to 142,500 anti-Xa IU.

***FRAXIPARINE FORTE*™ and *FRAXODI*™ [Nadroparin calcium Double Strength solution for injection (19,000 anti-Xa IU Ph.Eur./ml)]**

Graduated pre-filled syringes:

- 0.6 ml of solution equivalent to 11,400 anti-Xa IU
- 0.8 ml of solution equivalent to 15,200 anti-Xa IU
- 1 ml of solution equivalent to 19,000 anti-Xa IU.

Multi-dose Vials:

- 5 ml of solution equivalent to 95,000 anti-Xa IU.
- 15 ml of solution equivalent to 285,000 anti-Xa IU.

PHARMACEUTICAL FORM

Solution for injection.

CLINICAL PARTICULARS

Indications

FRAXIPARINE [Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)]

- The prophylaxis of thromboembolic disorders, such as:
  - those associated with general or orthopaedic surgery
  - those in high risk medical patients (respiratory failure and/or respiratory infection and/or cardiac failure), hospitalised in intensive care unit.
- The treatment of thromboembolic disorders.
- The prevention of clotting during haemodialysis.
- The treatment of unstable angina and non-Q wave myocardial infarction.

FRAXIPARINE FORTE* and *FRAXODI [Nadroparin calcium Double Strength solution for injection (19,000 anti-Xa IU/ml)]

- The treatment of thromboembolic disorders.

Dosage and Administration

Particular attention should be paid to the specific dosing instructions for each proprietary Low Molecular Weight Heparin, as different units of measurement (units or mg) are used to express doses. Nadroparin should therefore not be used interchangeably with other low molecular weight heparins during ongoing treatment. In addition, care should be taken to use the correct formulation of nadroparin, either single or double strength, as this will affect the dosing regimen.

Graduated syringes are intended for use when dose adjustment for body weight is necessary.

Nadroparin is not intended for intramuscular injection.

Platelet count must be monitored throughout nadroparin treatment (*see Warnings and Precautions*).

Specific recommendations regarding the timing of nadroparin dosing surrounding spinal/epidural anaesthesia or spinal lumbar puncture should be followed (*see Warnings and Precautions*).

Subcutaneous injection technique:

The usual site for subcutaneous injection is on the right or left side of the abdominal wall, but the thigh may be used as an alternative. To avoid loss of the solution when using pre-filled syringes, the air bubble should not be expelled from the syringe before the injection. The needle should be inserted perpendicularly into a pinched-up fold of skin which should be held gently but firmly until injection has been completed. The injection site should not be rubbed.

Populations

- **Adults**

PROPHYLAXIS OF THROMBOEMBOLIC DISORDERS

FRAXIPARINE [Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)]

- *General Surgery*

The recommended dose of *FRAXIPARINE* is 0.3 ml (2,850 anti-Xa IU) administered subcutaneously 2 to 4 hours before surgery, and then once daily on subsequent days. Treatment should be continued for at least seven days, and throughout the risk period, until the patient is ambulant.

- *Orthopaedic Surgery*

FRAXIPARINE is administered subcutaneously and the dose is adjusted for body weight according to the table below. This is based on a target dose of 38 anti-Xa IU per kg body weight, and is increased by 50% on the fourth post-operative day. The initial dose is administered 12 hours before surgery and a second dose 12 hours after the end of surgery. Treatment is then continued once daily throughout the risk period and until the patient is ambulant. The minimum treatment period is 10 days.

Body weight (kg)	**12 hours before and after surgery, and then once daily to the third post-operative day**		**From the fourth Post-operative day onwards**	
	Volume injected (ml)	**Anti-Xa IU**	**Volume injected (ml)**	**Anti-Xa IU**
<50	0.2	1,900	0.3	2,850
50-69	0.3	2,850	0.4	3,800
≥70	0.4	3,800	0.6	5,700

- *high-risk medical patients in intensive care (respiratory failure and/or respiratory infection and/or cardiac failure)*

FRAXIPARINE is administered subcutaneously once daily. The dose should be adjusted for body weight according to the table below. Treatment should be continued throughout the risk period of thromboembolism.

Body weight (kg)	**Once daily**	
	Volume injected (ml)	**Anti-Xa IU**
≤70	0.4	3,800
>70	0.6	5,700

TREATMENT OF THROMBOEMBOLIC DISORDERS

In the treatment of thromboembolic disorders, oral anticoagulant therapy should be initiated as soon as possible unless contraindicated. Treatment with *FRAXIPARINE* should not be stopped before the International Normalised Ratio target is reached.

FRAXIPARINE [Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)]

It is recommended that *FRAXIPARINE* is administered subcutaneously twice daily (every 12 hours) for a usual duration of 10 days. The dose should be adjusted for body weight according to the table below, which is based on a target dose of 86 anti-Xa IU per kg body weight.

Body weight (kg)	**Twice daily for a usual duration of 10 days**	
	Volume injected (ml)	**Anti-Xa IU**
<50	0.4	3,800
50-59	0.5	4,750
60-69	0.6	5,700
70-79	0.7	6,650
80-89	0.8	7,600
≥90	0.9	8,550

FRAXIPARINE FORTE and FRADOXI [Nadroparin calcium Double Strength solution for injection (19,000 anti-Xa IU/ml)]

It is recommended that *FRAXIPARINE FORTE* or *FRADOXI* is administered subcutaneously once daily for a usual duration of 10 days. The dose is adjusted to the patient's weight according to the table below, which is based on 171 anti-Xa IU per kg body weight.

Body weight (kg)	Once daily for a usual duration of 10 days	
	Volume injected (ml)	Anti-Xa IU
<50	0.4	7,600
50-59	0.5	9,500
60-69	0.6	11,400
70-79	0.7	13,300
80-89	0.8	15,200
≥90	0.9	17,100

PREVENTION OF CLOTTING DURING HAEMODIALYSIS

FRAXIPARINE [Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)]

In the prevention of clotting during haemodialysis, the dose of *FRAXIPARINE* must be optimised for each individual patient, also taking into account the technical conditions of the dialysis.

FRAXIPARINE is usually given as a single dose into the arterial line at the start of each session. For patients without increased risk of haemorrhage the following initial doses are suggested according to body weight and are usually sufficient for a four hour session:

Body weight (kg)	Injected into the arterial line at the start of dialysis	
	Volume injected (ml)	Anti-Xa IU
<50	0.3	2,850
50-69	0.4	3,800
≥70	0.6	5,700

Doses should be halved in patients with an increased risk of haemorrhage.

An additional smaller dose may be given during dialysis for sessions lasting longer than fourhours. The dose in subsequent dialysis sessions should be adjusted as necessary according to the observed effect.

Patients should be carefully monitored throughout each dialysis session for signs of bleeding or clotting in the dialysis circuit.

TREATMENT OF UNSTABLE ANGINA AND NON-Q WAVE MYOCARDIAL INFARCTION

FRAXIPARINE [Nadroparin calcium solution for injection (9,500 anti-Xa IU/ml)]

It is recommended that *FRAXIPARINE* is administered subcutaneously twice daily (every 12 hours). The usual duration of treatment is six days. In clinical studies in patients with

unstable angina and non-Q wave myocardial infarction, *FRAXIPARINE* was administered in combination with up to 325 mg aspirin per day.

The initial dose is administered as a bolus injection intravenous (i.v.) and subsequent doses given by subcutaneous injection. The dose should be adjusted for body weight according to the table below, which is based on a target dose of 86 anti-Xa IU per kg body weight.

Body weight (kg)	**Initial i.v. bolus**	**Subcutaneous injection (every 12 hours)**	**Anti-Xa IU**
< 50	0.4 ml	0.4 ml	3,800
50-59	0.5 ml	0.5 ml	4,750
60-69	0.6 ml	0.6 ml	5,700
70-79	0.7 ml	0.7 ml	6,650
80-89	0.8 ml	0.8 ml	7,600
90-99	0.9 ml	0.9 ml	8,550
≥ 100	1.0 ml	1.0 ml	9,500

- **Children and Adolescents**

Nadroparin is not recommended in children and adolescents as there are insufficient safety and efficacy data to establish dosage in patients aged less than 18 years.

- **Elderly**

No dosage adjustment is necessary in the elderly, unless renal function is impaired. It is recommended that renal function is assessed before initiating treatment (*see Renal Impairment below, and Pharmacokinetics*).

- **Renal Impairment**

Prophylaxis of thromboembolic disorders

Dose reduction is not required in patients with mild renal impairment (creatinine clearance greater than or equal to 50 ml/min).

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

If a dose reduction is considered appropriate by the prescribing physician, taking into account the individual risk factors for haemorrhage and thromboembolism in patients with moderate renal impairment (creatinine clearance greater than or equal

to 30 ml/min and less than 50 ml/min) the dose should be reduced by 25 to 33% (*see Warnings and Precautions and Pharmacokinetics*).

The dose should be reduced by 25 to 33% in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (*see Warnings and Precautions and Pharmacokinetics*).

Treatment of thromboembolic disorders, unstable angina and non-Q wave myocardial infarction

Dose reduction is not required in patients with mild renal impairment (creatinine clearance greater than or equal to 50 ml/min).

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

If a dose reduction is considered appropriate by the prescribing physician, taking into account the individual risk factors for haemorrhage and thromboembolism in patients with moderate renal impairment (creatinine clearance greater than or equal to 30 ml/min and less than 50 ml/min) the dose should be reduced by 25 to 33% *(see Warnings and Precautions and Pharmacokinetics).*

Nadroparin is contraindicated in patients with severe renal impairment (*see Warnings and Precautions and Pharmacokinetics*).

- **Hepatic impairment**

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

Contraindications

Nadroparin is contraindicated in cases of:

- hypersensitivity to nadroparin or any of the excipients of nadroparin injections
- history of thrombocytopenia with nadroparin (s*ee Warnings and Precautions*)
- active bleeding or increased risk of haemorrhage, in relation to haemostasis disorders, except for disseminated intravascular coagulation not induced by heparin
- organic lesion likely to bleed (such as active peptic ulceration)
- haemorrhagic cerebrovascular accident
- acute infectious endocarditis

- severe renal impairment (creatinine clearance less than 30 ml/min) in patients receiving treatment for thromboembolic disorders, unstable angina, and non-Q wave myocardial infarction

- multi-dose vials contain benzyl alcohol and therefore should not be used in children under 3 years.

Warnings and Precautions

Heparin-induced Thrombocytopenia

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

Rare cases of thrombocytopenia, occasionally 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 level (30 to 50% compared with the baseline value)

- worsening of the initial thrombosis while on therapy

- thrombosis occurring on 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 therapy, but may occur much earlier if there is a history of heparin-induced thrombocytopenia.

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

When thrombocytopenia occurs with heparin (either standard or low molecular weight heparin), substitution with a different antithrombotic class should be considered. If not available, then substitution with another low molecular weight heparin may be considered if the administration of heparin is necessary. In such cases, platelet count monitoring should be performed at least daily and the treatment should be discontinued as soon as possible, since cases of initial thrombocytopenia continuing after substitution have been described (*see Contraindications*).

In vitro platelet aggregation tests are 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 failure
- severe arterial hypertension
- history of peptic ulceration or other organic lesion likely to bleed
- vascular disorder of the chorio-retina
- during the post-operative period following surgery of the brain, spinal cord or eye.

Renal Impairment

Nadroparin is known to be mainly excreted by the kidney, which results in increased nadroparin exposure in patients with renal impairment *(see Pharmacokinetics – Renal Impairment).* Patients with impaired renal function are at increased risk of bleeding and should be treated with caution.

The decision on whether a dose reduction is appropriate for patients with creatinine clearance 30 to 50 ml/min should be based on the physician's assessment of an individual patient's risk of bleeding versus the risk of thromboembolism *(see Dosage and Administration).*

Elderly

It is recommended that renal function is assessed before initiating treatment (*see Contraindications*).

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 enzyme (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/epidural anaesthesia/spinal lumbar puncture and concomitant drugs

The risk of spinal/epidural haematomas is increased by in-dwelling epidural catheters or by the concomitant use of other drugs which may 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.

Therefore, the concomitant prescription of a neuraxial blockade and of an anticoagulant therapy should be decided after careful individual benefit/risk assessment in the following situations:

- in patients already treated with anticoagulants, the benefits of a neuraxial blockade must be carefully balanced against the risks.

- in patients planned to undergo elective surgery with neuraxial blockade, the benefits of anticoagulant therapy must be carefully balanced 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. For patients with renal impairment longer intervals may be considered.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

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

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.

In clinical studies for the treatment of unstable angina and non-Q wave myocardial infarction, nadroparin was administered in combination with up to 325 mg aspirin per day (*see Dosage and Administration*).

Cutaneous Necrosis

Cutaneous Necrosis has been reported very rarely. It is preceded by purpura or infiltrated or painful erythematous blotches, with or without general signs. In such cases, treatment should be immediately discontinued.

Latex Allergy

The needle shield of the pre-filled syringe may contain dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals**.**

Interactions

Nadroparin should be administered with caution in patients receiving oral anticoagulant agents, systemic (gluco-) corticosteroids and dextrans. When oral anticoagulant therapy is initiated in patients receiving nadroparin, treatment with nadroparin should be continued until the International Normalisation Ratio (INR) is stabilised at the target value.

Pregnancy and Lactation

Fertility

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

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. Therefore, the use of nadroparin during pregnancy is not advised, unless the therapeutic benefits outweigh the possible risks.

Lactation

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

Effects on Ability to Drive and Use Machines

There are no data on the effects of nadroparin on driving performance or the ability to operate machinery.

Adverse Reactions

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

The following convention has been used for the classification of adverse reactions in terms of frequency: Very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥1/1000 to <1/100, rare ≥1/10,000 to <1/1000, very rare <1/10,000.

Blood and lymphatic system disorders

Very common:	Haemorrhagic manifestations at various sites, more frequent in patients with other risk factors (*see Contraindications and Interactions*).

Rare: Thrombocytopenia, (including heparin-induced thrombocytopenia) (*see Warnings and Precautions*), thrombocytosis.

Very rare: Eosinophilia, reversible following treatment discontinuation.

Immune system disorders

Very rare: Hypersensitivity reactions (including angioedema and cutaneous reactions), anaphylactoid reaction.

Metabolism and nutrition disorders

Very rare: Reversible hyperkalaemia related to heparin-induced aldosterone suppression, particularly in patients at risk (*see Warnings and Precautions*).

Hepato-biliary disorders

Common: Raised transaminases, usually transient.

Reproductive system and breast disorders

Very rare: Priapism.

Skin and subcutaneous tissue disorders

Rare: Rash, urticaria, erythema, pruritus

Very rare: Cutaneous necrosis, usually occurring at the injection site (*see Warnings and Precautions*).

General disorders and administration site conditions

Very common: Small haematoma at the injection site.

In some cases, the emergence of firm nodules, which do not indicate an encystment of the heparin may be noted. These nodules usually disappear after a few days.

Common: Injection site reaction.

Rare: Calcinosis at the injection site.

Calcinosis is more frequent in patients with abnormal calcium phosphate product, such as in some cases of chronic renal failure.

Overdose

Symptoms and Signs

Haemorrhage is the major clinical sign of subcutaneous or intravenous overdosage. The platelet count and other coagulation parameters should be measured. Minor bleeding rarely requires specific therapy, and reducing or delaying subsequent doses of nadroparin is usually sufficient.

Treatment

The use of protamine sulphate should be considered only in serious cases. It largely neutralises the anticoagulant effect of nadroparin but some anti-Xa activity will remain.

0.6 ml of protamine sulphate neutralises about 950 IU 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

B01AB06

Mechanism of Action

Pharmacotherapeutic group: Antithrombotic agents - Heparin group.

Nadroparin is a low molecular weight heparin made by depolymerisation of standard heparin. It is a glycosaminoglycan with a mean molecular weight of approximately 4300 daltons.

Nadroparin exhibits a high-affinity binding to the plasma protein anti-thrombin III (ATIII). This binding leads to an accelerated inhibition of factor Xa, which contributes to the high antithrombotic potential of nadroparin.

Other mechanisms that contribute to the antithrombotic activity of nadroparin include stimulation of tissue factor pathway inhibitor (TFP1), activation of fibrinolysis via direct release of tissue plasminogen activator from endothelial cells, and the modification of haemorrheological parameters (decreased blood viscosity and increased platelet and granulocyte membrane fluidity).

Pharmacodynamic Effects

Nadroparin has a high ratio of anti-Xa to anti-IIa activity. It has both immediate and prolonged antithrombotic action.

Compared with unfractionated heparin, nadroparin has less effect on thrombocyte function and aggregation and only a slight effect on primary haemostasis.

Pharmacokinetics

The pharmacokinetic properties of nadroparin have been assessed on the basis of biological activity, i.e. measurement of anti-factor Xa activity.

Absorption

Following subcutaneous administration, the peak anti-Xa activity (C_{max}) is reached after approximately 3 to 5 hours (T_{max}).

Bioavailability is almost complete (around 88%).

After i.v. injection, the peak plasma anti-Xa level is reached within less than 10 minutes, and the half-life is around 2 hours.

Elimination

The elimination half-life after subcutaneous injection is approximately 3.5 hours. However, anti-Xa activity is detectable for at least 18 hours following an injection of 1900 anti-Xa IU.

Special Patient Populations

Elderly

Renal function generally decreases with age so elimination is slower in the elderly (*see Pharmacokinetics: Renal Impairment below*). The possibility of renal impairment in this age group must be considered and the dosage adjusted accordingly (*see Dosage and Administration, Warnings and Precautions).*

Renal Impairment

In a clinical study investigating the pharmacokinetics of nadroparin administered intravenously in patients with varying degrees of renal impairment, a correlation was found between nadroparin clearance and the creatinine clearance. In patients with moderate renal impairment (creatinine clearance 36-43 ml/min), both mean AUC and half-life were increased by 52 and 39% respectively compared with healthy volunteers. In these patients, mean plasma clearance of nadroparin was decreased to 63% of normal. Wide inter-individual variability was observed in the study. In subjects with severe renal

impairment (creatinine clearance 10-20 ml/min) both mean AUC and half-life were increased by 95 and 112% respectively compared with healthy volunteers. Plasma clearance in patients with severe renal impairment was decreased to 50% of that observed in patients with normal renal function. In subjects with severe renal impairment (creatinine clearance 3-6 ml/min) on haemodialysis, both mean AUC and half-life were increased by 62 and 65% respectively compared with healthy volunteers. Plasma clearance in haemodialysis patients with severe renal impairment was decreased to 67% of that observed in patients with normal renal function (*see Dosage and Administration, Warnings and Precautions*).

Pre-clinical Safety Data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, mutagenic potential and reproductive toxicology.

PHARMACEUTICAL PARTICULARS

List of Excipients

Pre-filled syringes

Calcium hydroxide solution or dilute hydrochloric acid for pH adjustment (5 to 7.5).

Water for injections.

Multi-dose vials

Calcium hydroxide solution or dilute hydrochloric acid for pH adjustment (5 to 7.5).

Water for injections.

Benzyl alcohol (9 mg/ml) as a preservative.

Incompatibilities

Do not mix with other products.

Shelf-Life

3 years.

The shelf-life after opening the multi-dose vials is 28 days at room temperature.

Special Precautions for Storage

Do not freeze. Do not refrigerate as cold injections may be painful.

***FRAXIPARINE* [Nadroparin calcium solution for injection (9,500 anti-Xa IU Ph.Eur./ml)]:**

Do not store above 30°C.

***FRAXIPARINE FORTE* and *FRAXODI* [Nadroparin calcium Double Strength solution for injection (19,000 anti-Xa IU Ph.Eur./ml)]:**

Pre-filled syringes

Do not store above 30°C.

Multi-dose vials

Do not store above 25°C.

Nature and Contents of Container

FRAXIPARINE TM. syringe presentations has 10 pre-filled syringes in carton pack.

Instructions for Use/Handling

See *Dosage and Administration.*

Nadroparin should be visually inspected for any particulate matter and discoloration before use. If any visual change is noted, the solution must be discarded.

Syringes are intended for single use only, and any unused portion of each syringe must be discarded. Solutions must not be mixed with other preparations or re-dispensed.

After administration the needle guard must be slid over the exposed needle, so that the needle is completely covered. The syringe can then be disposed of appropriately.

The plastic "flip off" cap must be removed from multi-dose vials, and only the middle of the aluminium cap removed, so that the small circle on the rubber stopper is visible. The rubber stopper must be disinfected before inserting the needle.

Not all presentations are available in every country.

Instructions for self administration using a pre-filled syringe

Always use *TRADENAME* exactly as your doctor or nurse has instructed you. You should ask their advice if you are having any difficulties injecting *TRADENAME*.

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

2. **Sit or lie down in a comfortable position.**

   The injection is given in the side of the lower stomach area (figure 1). **Alternate the left and right side** of the stomach at each injection.

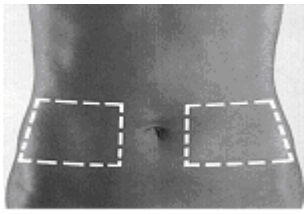

Figure 1

3. **Clean the injection area with an alcohol swab.**

4. **Pull off the cap** that protects the needle. **Discard the cap.**

   If the volume in the syringe is more than you need, you must remove the excess **before you** inject yourself.

   - Hold the syringe with the needle pointing straight down.
   - Push the syringe plunger gently down until the bottom of the bubble sits on the line marked with the volume your doctor has prescribed for you.
   - Drip the fluid that comes out of the needle on to a tissue, and discard.
   - The syringe is now ready to use.

   Important note:

   - **Do not touch the needle** or allow it to come in contact with any surface before the injection
   - The presence of a small air bubble in the syringe is normal. **Do not try to remove this air bubble before making the injection.**

5. **Gently pinch the skin that has been cleaned to make a fold.** Hold the fold between the thumb and the forefinger during the entire injection (figure 2).

Figure 2

6. **Hold the syringe firmly by the finger hold.** Insert the full length of the needle straight (at an angle of 90˚) into the skin fold (figure 3).

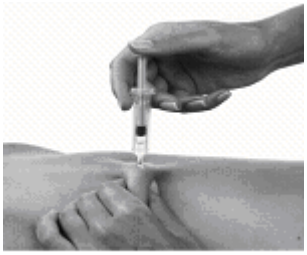

Figure 3

7. **Inject ALL of the contents of the syringe by pressing down on the plunger as far as it goes.**

8. Remove the syringe from the skin (figure 4). The injection site should not be rubbed.

Figure 4

9. **After injection use the safety shield to protect from needle injuries. To do this, hold the syringe in one hand by gripping the safety shield, then use the other hand to pull firmly on the finger hold.** This unlocks the shield. Slide the shield up the body of the syringe until it locks into position over the needle.

10. **Do not dispose of the used syringe in household waste**. Dispose of the used syringe as your nurse or doctor has instructed you.

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