1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FRAXIPARINE 0,2 ml (1 900 anti-Xa IU/0,2 ml)

FRAXIPARINE 0,3 ml (2 850 anti-Xa IU/0,3 ml)

FRAXIPARINE 0,4 ml (3 800 anti-Xa IU/0,4 ml)

FRAXIPARINE 0,6 ml (5 700 anti-Xa IU/0,6 ml)

FRAXIPARINE 0,8 ml (7 600 anti-Xa IU/0,8 ml)

FRAXIPARINE 1 ml (9 500 anti-Xa IU/ml)

Sterile solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1,0 ml of FRAXIPARINE solution contains 9 500 anti-Xa IU/ml nadroparin calcium.

Pre-filled syringes:

Each 0,2 ml of FRAXIPARINE contains 0,2 ml of solution equivalent to 1 900 anti-Xa IU nadroparin calcium.

Each 0,3 ml of FRAXIPARINE contains 0,3 ml of solution equivalent to 2 850 anti-Xa IU nadroparin calcium.

Each 0,4 ml of FRAXIPARINE contains 0,4 ml of solution equivalent to 3 800 anti-Xa IU nadroparin calcium.

Graduated pre-filled syringes:

Each 0,6 ml of FRAXIPARINE contains 0,6 ml of solution equivalent to 5 700 anti-Xa IU nadroparin calcium.

Each 0,8 ml of FRAXIPARINE contains 0,8 ml of solution equivalent to 7 600 anti-Xa IU nadroparin calcium.

Each 1,0 ml of FRAXIPARINE contains 1,0 ml of solution equivalent to 9 500 anti-Xa IU nadroparin calcium.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Pre-filled syringes and graduated pre-filled syringes:

FRAXIPARINE is a clear to slightly opalescent, colourless or slightly yellow solution.

Fraxiparine is a sterile preservative-free solution for subcutaneous injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

FRAXIPARINE is indicated for:

1. Prophylaxis of DVT (Deep Vein Thrombosis) which may lead to pulmonary embolism.
    - in patients undergoing hip or knee replacement surgery.
    - in patients undergoing abdominal surgery who are at risk of thromboembolic complications.

Patients at risk include patients who are over 40 years of age, obese, undergoing surgery under general anaesthesia lasting longer than 30 minutes or who have additional risk factors such as malignancy or a history of DVT or pulmonary embolism.

2. The prophylaxis of thromboembolic disorders, such as those in high risk medical patients (respiratory failure and/or respiratory infection and/or cardiac failure), immobilised due to acute illness or hospitalised in an intensive care unit.
3. The treatment of DVT (Deep Vein Thrombosis).

4.2. Posology and method of administration

FRAXIPARINE SHOULD BE ADMINISTERED BY THE SUBCUTANEOUS ROUTE ONLY.

Posology

Adults

Prophylaxis of (DVT) Deep Vein Thrombosis which may lead to pulmonary embolism in patients undergoing abdominal surgery:

FRAXIPARINE should be given as a dose of 0,3 ml (2 850 IU AXa anti-Xa IU) administered subcutaneously 2 to 4 hours before surgery and again 8 hours after surgery. Subsequent injections of 0,3 ml (2 850 IU AXa anti-Xa IU) should be administered once daily for at least 7 days after surgery. In all cases prophylaxis should be continued throughout the risk period and at least until the patient is ambulant.

Prophylaxis of Deep Vein Thrombosis which may lead to pulmonary embolism in patients undergoing hip or knee replacement surgery:

Initial doses should be given 12 hours before surgery and a second dose 12 hours after the end of surgery.

These and subsequent once-daily doses should be adjusted according to the body weight of the patient. The recommended dosage is 38 IU anti-Xa/kg for day 1 to 3 and 57 IU anti-Xa/kg from day 4 onwards. The table below can be used as a guide to the volumes to be injected. Treatment should be for at least 10 days and should continue in all cases throughout the risk period until the patient is ambulant.

Prophylaxis of DVT		
Hip or Knee Replacement Surgery	Volume to be injected subcutaneously once daily	
Body weight (kg)	Pre-operatively And until Day 3	From Day 4 onwards
45-60	0,2 ml	0,3 ml
61-74	0,3 ml	0,4 ml
75-80	0,3 ml	0,5 ml
80-90	0,4 ml	0,5 ml
90-100	0,4 ml	0,6 ml

No safe or effective doses in patients under 45 or over 100 kg have been established.

High-risk medical patients (respiratory failure and/or respiratory infection and/or cardiac failure), immobilised due to acute illness or hospitalised in an intensive care unit.

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

In elderly patients, dose reduction to 0,3 ml (2,850 anti-Xa IU) may be appropriate.

Treatment of Deep Vein Thrombosis (DVT):

FRAXIPARINE should be given subcutaneously twice daily (every 12 hours) for a usual duration of 10 days with the dose adjusted to body weight as shown below:

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

Special populations

Elderly population

A dose adaptation for elderly patients is not necessary unless in the presence of renal failure. It is recommended that renal function is assessed before initiating treatment (see section 5.2).

The prophylaxis of thromboembolic disorders, such as:

- those in high risk medical patients (respiratory failure and/or respiratory infection and/or cardiac failure), immobilised due to acute illness or hospitalised in an intensive care unit.

In elderly patients, dose reduction to 0,3 ml (2,850 anti-Xa IU) may be appropriate.

Renal impairment

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

-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 IU 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 haemorrhage 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).

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

Hepatic impairment

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

Paediatric population

FRAXIPARINE should not be administered to children under 18 years of age.

The safety and efficacy of FRAXIPARINE in children aged below 18 years has not yet been established (see section 4.3).

Method of administration

Subcutaneous injection.

The usual site for subcutaneous injection is the lateral abdominal wall, although the thigh may be used as an alternative.

The needle should be inserted perpendicularly into a pinched-up fold of skin which should be held gently but firmly until the injection has been completed. Do not rub the injection site.

FRAXIPARINE is not intended for IM or IV administration.

***Removal of packaging prior to administration*:**

To divide the syringes, carefully fold the twin pack several times so that the syringes are back to back, then slowly, using an even pressure, divide the two syringes starting from the plunger end of the pack.

To remove the syringe from its plastic packaging, gently tear the top plastic film backing completely from the plastic tray (starting from the plunger end), then allow the syringe to roll into the palm of your other hand.

The rubber cap of the needle may appear to be asymmetrical on the syringe; however, this occurs during packaging and does not mean that the needle is bent.

Preparation of the syringe for subcutaneous injection:

To remove the cap from the syringe needle:

Hold the syringe vertically (grey cap uppermost). Hold the grey cap by its collar, and the syringe barrel in your other hand, then slowly rotate the syringe barrel gently pulling downwards at the same time, until the needle is fully withdrawn from the cap. Do not pull the cap upwards from the syringe as this may bend the needle.

FRAXIPARINE 0,2 ml (1 900 anti-Xa IU), FRAXIPARINE 0,3 ml (2 850 anti-Xa IU) and FRAXIPARINE 0,4 ml (3 800 anti-Xa IU) pre-filled syringes are intended for administration of unit dosages only. The entire contents of the syringe should be injected. There may be a small air bubble in the syringe but this does not have to be removed.

FRAXIPARINE 0,6 ml (5 700 anti-Xa IU), FRAXIPARINE 0,8 ml (7 600 anti-Xa IU) and FRAXIPARINE 1,0 ml (9 500 anti-Xa IU) pre-filled graduated syringes may be used to administer adjusted dosages. Hold the syringe vertically with the needle uppermost and ensure the air bubble is at the top of the syringe. Advance the plunger to the volume dosage required, expelling air and any excess.

***Method for subcutaneous administration*:**

1. A suitable site for injection is the subcutaneous tissue of the lateral abdominal wall, away from any wound or weight bearing site**.** Alternatively, injection may be made into the thigh (Fig. 1).

2. Pinch a skin fold (Fig. 2).

Note: the use of alcohol may toughen the skin, making subsequent injection difficult.

3. Maintain the fold and insert the needle vertically to its full depth, then inject FRAXIPARINE over 10-15 seconds (Fig. 3 and 4).

4. Still holding the skin fold, withdraw the needle vertically.

Do not rub the site of the injection (Fig. 5).

FRAXIPARINE is not intended for IM or IV administration.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

4.3. Contraindications

FRAXIPARINE is contraindicated in:

- Patients with hypersensitivity to nadroparin calcium, unfractionated heparin, any other low molecular weight heparin or any of the excipients of FRAXIPARINE, especially when severe thrombocytopenia has occurred in recent months.
- Haemorrhagic blood disorders - especially thrombocytopenia and haemophilia.
- Haemorrhage, active or suspected - especially cerebrovascular and gastrointestinal, except in disseminated intravascular coagulation not induced by heparin, FRAXIPARINE or a low molecular weight heparin.
- Acute infectious endocarditis.
- Children under 18 years (see section 4.2).
- Conditions where haemorrhage is a particular risk:
  - Aneurysm, cerebral or aortic.
  - Hypertension, severe or uncontrolled.
  - Threatened abortion.
  - Recent childbirth.
  - Infective endocarditis.
  - Pericarditis.

- Vasculitis, severe.
- Active, cavitating tuberculosis.
- Visceral carcinoma.
- Any intracranial tumour, either primary or secondary.
- During or after eye, brain or spinal cord surgery or trauma.
- Prior to lumbar puncture or regional anaesthetic block.
- Active peptic ulceration.
- Surgical or traumatic wounds resulting in large open surfaces.

- Severe renal function impairment, (creatinine clearance less than 30 ml/min) in patients receiving treatment for thromboembolic disorders (see section 4.2).
- Severe hepatic function impairment.
- Mechanical heart valve prosthesis.
- Pregnancy and lactation as safety and efficacy has not been demonstrated (see section 4.6).

4.4. Special warning and precautions for use

Heparin-induced thrombocytopenia:

FRAXIPARINE is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia, with or without thrombosis. The risk of heparin-induced thrombocytopenia may persist for several years. If a history of heparin-induced thrombocytopenia is suspected, the decision to use FRAXIPARINE in such a case must be made only in consultation with an expert in the field.

The low molecular weight heparins are not shown to be absolutely biologically or therapeutically equivalent. As they differ from one another in having different molecular weight profiles, different specific activities (Anti-Xa to Anti IIa activities),

different rates of plasma clearance, different dosage regimes etc., they cannot be accepted as therapeutically equivalent.

Cross-reactivity

Cross-reactivity between heparins and LMWH is well documented. Delayed hypersensitivity reactions have been reported in patients presenting cross-reactivity between unfractionated heparins and LMWH.

Before initiating therapy with low molecular weight heparins (LMWH), careful assessment should be made concerning previous hypersensitivity reactions to unfractionated heparin.

Hypersensitivity

FRAXIPARINE should be used with caution in patients with a history of allergic reactions especially to heparin and low molecular weight heparins, in such cases a test dose may be administered.

Generalised allergic reactions, including angioedema and skin allergic reactions may occur.
Cases of cutaneous necrosis, usually occurring at the injection site, have been reported with FRAXIPARINE; they are usually preceded by purpura or infiltrated or painful erythematous blotches, with or without general signs (see section 4.8). Treatment with FRAXIPARINE should be discontinued immediately.
Subcutaneous haematoma at the injection site. Pain and bruising are minimised by careful injection technique. 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.

Lumbar puncture, spinal or epidural anaesthesia are contraindicated in patients who receive curative treatment with nadroparin due to the risk of haematoma 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 anaesthesia. The risk of a spinal/epidural haematoma is increased by an epidural indwelling catheter or by the simultaneous administration of other medicines 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 anaesthetic 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 FRAXIPARINE 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 anaesthesia, 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 FRAXIPARINE 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 should they experience one of these symptoms.

If signs or symptoms of spinal haematoma 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.

Platelet count monitoring

Thrombocytopenia may occur. Two forms of thrombocytopenia have been identified. The first is a mild form occurring on the second to fourth day of heparin use, and which may improve despite continued heparin administration. It is characterised by a moderate decrease in platelet count and an absence of thrombotic or haemorrhagic complications. The second is a severe form associated with the development of antiplatelet aggregating antibodies. It is associated with very low platelet counts and thrombotic complications including organ infarction, skin necrosis, gangrene of the extremities, pulmonary embolism and stroke.

Because of the possibility of heparin-induced thrombocytopenia, regular monitoring of platelet count should be done throughout the course of treatment with FRAXIPARINE. FRAXIPARINE has shown to have cross-reactivity with heparins and low molecular weight heparins with regard to thrombocytopenia, and should not be used in patients with a history of thrombocytopenia associated with any heparin preparation (see bold text - Cross-reactivity).

Rare cases of thrombocytopenia, occasionally severe, have been reported; they may be associated with arterial or venous thrombosis. FRAXIPARINE should be discontinued immediately. Such diagnosis should be considered in the following cases:

- thrombocytopenia (< 100 000/mm^3)
- any significant decrease in platelet count: 30 to 50 % of the baseline value
- worsening of the initial thrombosis while on therapy
- thrombosis occurring on treatment
- disseminated intravascular coagulation.

These effects may sometimes be of immuno-allergic nature but may occur in case of a first treatment when they are reported mainly between the 5^{th} and the 21^{st} day of therapy. Thrombocytopenia aroused by hypersensitivity may occur much earlier if there is a history of heparin-associated thrombocytopenia, in patients previously exposed to heparin or other low molecular weight heparins.

Where there is a history of thrombocytopenia occurring with heparin (either standard or low molecular weight heparin), a treatment with FRAXIPARINE should be carefully considered if the administration of heparin is necessary; in such case, careful clinical monitoring and

assessment of platelet count should be performed at least daily. If thrombocytopenia occurs, treatment should be discontinued immediately since early recurrences have been reported. Substitution with FRAXIPARINE should not be considered where thrombocytopenia has occurred with another heparin or low molecular weight heparin as thrombocytopenia continuing after substitution has been frequently observed.

Renal impairment

FRAXIPARINE is mainly excreted by the kidney, which results in increased FRAXIPARINE exposure in patients with renal impairment (see section 5.2).

Patients with severely impaired renal function are at increased risk of bleeding and should be treated with caution.

It is recommended that a test dose be given as a check for FRAXIPARINE sensitivity.

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).

Elderly

It is recommended to check the kidney function before starting treatment (see section 4.3). Doses must be reduced in the elderly. Women over 60 years are especially susceptible to FRAXIPARINE toxicity.

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.

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 such cases, treatment should be immediately discontinued.

Bleeding

The most common complication is bleeding. Reduction of this complication to a minimum can be effected by careful laboratory control. However as the effect of FRAXIPARINE is predominantly on factor Xa and not on factor IIa, as with unfractionated heparin, the APTT test alone is insufficient to monitor the effects of FRAXIPARINE. The laboratory test for the anti-Xa effect is not routinely available in most laboratories but is the only test to determine effects of FRAXIPARINE.

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

- hepatic failure

- history of peptic ulceration or other organic lesion likely to bleed
- vascular disorder of the chorio-retina
- severe arterial hypertension
- during the post-operative period following surgery of the brain, spinal cord or eye
- simultaneous treatment with oral anticoagulants.

4.5. Interaction with other medicines and other forms of interaction

FRAXIPARINE should be used with care in conjunction with oral anticoagulants.

When oral anticoagulant therapy is initiated in patients receiving FRAXIPARINE, treatment with FRAXIPARINE should be continued until the International Normalisation Ratio (INR) is stabilised at the target value.

FRAXIPARINE should be used with care in conjunction with the following:

- medicines which affect platelet function such as aspirin, dipyridamole, ibuprofen and indomethacin,
- dextran injections,
- thrombolytic enzymes such as streptokinase.

Digitalis, tetracyclines, nicotine or antihistamines may partly counteract the anticoagulant action of FRAXIPARINE.

Careful monitoring of partial thromboplastin time and the anti Xa-effects and adjustment of FRAXIPARINE doses are recommended during co-administration of FRAXIPARINE and IV nitroglycerine.

4.6. Fertility, pregnancy and lactation

The safety of FRAXIPARINE in pregnancy and lactation has not been established (see section 4.3).

Pregnancy

Women should not take FRAXIPARINE during pregnancy.

Studies in animals have not shown any teratogenic or foetotoxic effects. However, there is only limited clinical data concerning transplacental passage of FRAXIPARINE in pregnant women.

Breastfeeding

Women should not breastfeed their infants when taking FRAXIPARINE.

There is limited information on the excretion of FRAXIPARINE in breast milk.

Fertility

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

4.7. Effects on ability to drive and use machines

FRAXIPARINE has no or negligible influence on the ability to drive and use machines. Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that FRAXIPARINE does not adversely affect their ability to do so safely.

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Blood and the lymphatic	Haemorrhagic manifestations[1]	Thrombocytopenia, heparin-induced	

system disorders		thrombocytopenia, thrombocytosis, eosinophilia (reversible following treatment discontinuation).	
Immune system disorders		Hypersensitivity reactions (including angioedema and cutaneous reactions), anaphylactoid reaction.	
Metabolism and nutrition disorders		Reversible hyperkalaemia related to heparin-induced aldosterone suppression particularly in patients at risk, rebound hyperlipidaemia following discontinuation of FRAXIPARINE.	
Nervous system disorders			Headache, migraine.
Skin and subcutaneous tissue disorders		Rash, urticaria, erythema, pruritis.	
Musculoskeletal and connective tissue disorders		Risk of osteoporosis as well as spontaneous and compression fractures.	
Reproductive system and breast disorders		Priapism.	
General disorders and administrative site conditions	Injection site haematoma[2].	Injection site calcification[3], injection site necrosis.	
Investigations	Transaminases increased, usually transient		

1. Haemorrhagic manifestations at various sites, more frequent in patients with other risk factors.
2. 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.
3. Calcification is more frequent in patients with abnormal calcium phosphate product, such as in some cases of chronic renal failure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to **SAHPRA** via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ +27 (0)11 239-6200

4.9. Overdose

Symptoms

The protraction of the activated Partial Thromboplastin Time (aPTT) value should be considered only as the extent of the overdose 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

The use of protamine sulphate should be considered only in serious cases. It largely neutralises the anticoagulant effect of FRAXIPARINE but some anti-Xa activity will remain. 0,6 ml of protamine sulphate neutralises about 950 anti-Xa IU FRAXIPARINE. 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

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 depolymerisation of standard heparin. Structurally, this is a glycosaminoglycan.

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

Category and Class: A 8.2 Anticoagulants

Pharmacotherapeutic group: Medicines acting on blood and haemopoietic system

ATC code: B01AB06

Mechanism of action

FRAXIPARINE has antithrombotic activity.

Nadroparin exerts its anticoagulant activity by accelerating the inhibition of several coagulant factors, in particular factors Xa and IIa, by ATIII. Once activated, ATIII inhibits factor Xa about 1000 times more rapidly than the non-activated form. The ATIII-mediated ability of nadroparin to inactivate factor Xa depends only on the presence of the pentasaccharide binding site with the nadroparin molecule. In contrast, with regard to the ATIII-mediated ability of nadroparin to inactivate thrombin, nadroparin molecules need to bind both ATIII and thrombin in order to facilitate the interaction between thrombin and ATIII. Therefore, only chains with the pentasaccharide site and sufficiently large to accommodate thrombin and ATIII (i.e. 18 saccharides or 5400 Daltons) are able to elicit an anti-IIa activity. Approximately 15% of nadroparin molecules fulfil this condition.

In platelet-poor plasma, nadroparin inhibits thrombin generation in a dose-dependent manner. Through its ATIII mediated anti-IIa effect, nadroparin scavenges the initial traces of thrombin, thereby reducing factor V activation and subsequent prothrombinase formation. The ability of nadroparin to inhibit thrombin generation is more a consequence of its anti-IIa activity rather than its anti-Xa activity. Nadroparin also inhibits thrombin generation in the presence of platelets. Under this condition, in addition to activating factor V, thrombin induces platelet aggregation, which leads to the subsequent release of platelet factor 4 (PF4). This highly basic polypeptide interacts with nadroparin chains above 5400 Daltons, i.e., those with anti-IIa activity. Consequently, the anti-IIa effect of nadroparin is rapidly overwhelmed, and prothrombin activation may occur. However, prothrombinase formation and the amount of thrombin generated are attenuated by the anti-Xa activity borne by low-molecular weight chains of nadroparin, which are unaffected by PF4.

AXa denotes anti-factor Xa activity (in international units). The ratio of anti-Xa to anti-IIa activity of nadroparin calcium is 2,5 to 4,0.

Nadroparin calcium is a low molecular weight heparin manufactured by depolymerisation of standard heparin. It is a glycosaminoglycan with a mean molecular weight of approximately 4300 daltons. It is derived from porcine heparin.

5.2. Pharmacokinetic properties

Pharmacokinetics have been determined by measurement of plasma anti-Xa activity.
The plasma peak occurs about 3 hours after subcutaneous injection. Some anti-Xa activity persists for at least 18 hours after administration.

Absorption

The maximum anti-Xa activity (c_{max}) is achieved approx. 3 hours (t_{max}) after subcutaneous injection.

Distribution

The bioavailability with regard to the anti-Xa activity is almost complete (approx. 88 %).

Elimination

The elimination half-life is about 3,5 hours in normal young volunteers.

The excretion is principally renal, and in patients with impaired renal function, a reduced dosage should be considered as elimination of Axa activity is prolonged in such patients.

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 to 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 to 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 to 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 section 4.2 and 4.4*)*.

Elderly patients

Renal function generally decreases with age so elimination is slower in the elderly. The possibility of renal impairment in this age group must be considered and the dosage adjusted accordingly (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment), water for injection.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Pre-filled syringes and graduated pre-filled syringes:

Store at or below 25 °C.

Do not freeze.

Discard any unused portion of each syringe.

Do not refrigerate, as the injection of cold injections may be painful. Do not mix with other preparations.

Do not use after the expiry date.

6.5. Nature and contents of container

FRAXIPARINE 0,2 ml

FRAXIPARINE 0,3 ml

FRAXIPARINE 0,4 ml

0,2 ml, 0,3 ml and 0,4 ml: Sterile Solution for Injection in 1 ml unit dose ungraduated pre-filled glass syringes, presented in cartons containing two or ten syringes.

FRAXIPARINE 0,6 ml

FRAXIPARINE 0,8 ml

FRAXIPARINE 1,0 ml

0,6 ml; 0,8 ml and 1,0 ml: Sterile Solution for Injection in 1 ml graduated pre-filled glass syringes, presented in cartons containing two or ten syringes.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

See section 4.2 Posology and method of administration.

Nadroparin solution for injections 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 shield must be slid over the exposed needle, so that the needle is completely covered. The syringe can then be disposed of appropriately.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBERS

FRAXIPARINE 0,2 ml: 31/8.2/0576

FRAXIPARINE 0,3 ml: 31/8.2/0577

FRAXIPARINE 0,4 ml: 31/8.2/0578

FRAXIPARINE 0,6 ml: 31/8.2/0579

FRAXIPARINE 0,8 ml: 31/8.2/0580

FRAXIPARINE 1 ml: 31/8.2/0581

9. DATE OF FIRST AUTHORISATION

Date of registration:

FRAXIPARINE 0,2 ml: 11 October 2000

FRAXIPARINE 0,3 ml: 10 October 2000

FRAXIPARINE 0,4 ml: 10 October 2000

FRAXIPARINE 0,6 ml: 10 October 2000

FRAXIPARINE 0,8 ml: 10 October 2000

FRAXIPARINE 1 ml: 25 February 2000

10. DATE OF REVISION OF TEXT

26 March 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

Namibia:	NS2
0,2 ml	05/8.2/0013
0,3 ml	05/8.2/0014
0,4 ml	05/8.2/0016
0,6 ml	05/8.2/0017
0,8 ml	05/8.2/0018
1 ml	05/8.2/0019

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