1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

FRAXIPARINE 0,2 ml (solution for injection)

FRAXIPARINE 0,3 ml (solution for injection)

FRAXIPARINE 0,4 ml (solution for injection)

FRAXIPARINE 0,6 ml (solution for injection)

FRAXIPARINE 0,8 ml (solution for injection)

FRAXIPARINE 1,0 ml (solution for injection)

COMPOSITION

FRAXIPARINE is a sterile clear preservative-free solution for subcutaneous injection.

Each 0,2 ml of FRAXIPARINE 0,2 ml contains nadroparin calcium 1 900 IU AXa.

Excipient:

Water for injection

Sugar free

Each 0,3 ml of FRAXIPARINE 0,3 ml contains nadroparin calcium 2 850 IU AXa.

Excipient:

Water for injection

Sugar free

Each 0,4 ml of FRAXIPARINE 0,4 ml contains nadroparin calcium 3 800 IU AXa.

Excipient:

Water for injection

Sugar free

Each 0,6 ml of FRAXIPARINE 0,6 ml contains nadroparin calcium 5 700 IU AXa.

Excipient:

Water for injection

Sugar free

Each 0,8 ml of FRAXIPARINE 0,8 ml contains nadroparin calcium 7 600 IU AXa.

Excipient:

Water for injection

Sugar free

Each 1,0 ml of FRAXIPARINE 1,0 ml contains nadroparin calcium 9 500 IU AXa.

Excipient:

Water for injection

Sugar free

CATEGORY AND CLASS

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 4 500 daltons. It is derived from porcine heparin.

Nadroparin calcium has antithrombotic activity.

Pharmacokinetic properties

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.

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.

Pharmacokinetics have been determined by measurement of plasma anti-Xa activity.

The plasma peak occurs about 3 hours after subcutaneous injection. The elimination half-life is about 3,5 hours in normal young volunteers. Some anti-Xa activity persists for at least 18 hours after administration. Bioavailability is almost complete.

INDICATIONS

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.

Treatment of DVT (Deep Vein Thrombosis).

CONTRAINDICATIONS

- Known hypersensitivity to nadroparin calcium, unfractionated heparin, any other low molecular weight heparin, 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, nadroparin calcium or a low molecular weight heparin.
- Children.
- 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;

- severe hepatic function impairment;
- mechanical heart valve prosthesis.

- Pregnancy and lactation, as safety and efficacy has not been demonstrated.

WARNINGS AND SPECIAL PRECAUTIONS

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.

Special precautions:

Patients with severely impaired liver or kidney function are at risk of haemorrhage. It is recommended that a test dose be given as a check for FRAXIPARINE sensitivity.

Doses must be reduced in the elderly. Women over 60 years are especially susceptible to FRAXIPARINE toxicity.

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.

Platelet count monitoring:

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.

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), 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.

INTERACTIONS

FRAXIPARINE should be used with care in conjunction with oral anticoagulants, medicines which affect platelet function such as aspirin, dipyridamole, ibuprofen and indomethacin, dextran injections and 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.

HUMAN REPRODUCTION

Safety and efficacy has not been demonstrated in pregnancy and lactation (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

FRAXIPARINE SHOULD BE ADMINISTERED BY THE SUBCUTANEOUS ROUTE ONLY.

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) administered 2 hours before surgery and again 8 hours after surgery. Subsequent injections of 0,3 ml (2 850 IU AXa) 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 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 U 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 to 60	0,2 ml	0,3 ml
61 to 74	0,3 ml	0,4 ml
75 to 80	0,3 ml	0,5 ml
80 to 90	0,4 ml	0,5 ml
90 to 100	0,4 ml	0,6 ml

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

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:

Treatment of DVT	
Body weight (kg)	Volume of FRAXIPARINE to be injected subcutaneously twice daily
< 50 50 to 59 60 to 69 70 to 79 80 to 89 = 90	0,4 ml 0,5 ml 0,6 ml 0,7 ml 0,8 ml 0,9 ml

Oral anticoagulant therapy is initiated as soon as possible unless there is a contraindication. Treatment with FRAXIPARINE should not be stopped before INR target is reached.

Administration:

FRAXIPARINE is given only by subcutaneous injection. The usual site for 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 IU AXa), FRAXIPARINE 0,3 ml (2 850 IU AXa) and FRAXIPARINE 0,4 ml (3 800 IU AXa) 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 IU AXa), FRAXIPARINE 0,8 ml (7 600 IU AXa) and FRAXIPARINE 1,0 ml (9 500 IU AXa) 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 to 15 seconds (Fig. 3 & 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

SIDE EFFECTS

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.

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.

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. 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.

The following events may also occur:

- Eosinophilia, usually reversible following treatment discontinuation;
- rebound hyperlipaemia following discontinuation of FRAXIPARINE;
- raised transaminases;
- exceptionally, priapism and cases of reversible hypoaldosteronism either asymptomatic or associated with significant hyperkalaemia and/or hypernatraemia have been observed.

A risk of osteoporosis as well as spontaneous and compression fractures and alopecia with

long-term use (more than 6 weeks) may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

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

There is no clinical experience on the use of protamine sulphate to neutralise the effect of FRAXIPARINE overdosage.

IDENTIFICATION

Syringe containing a clear to slightly opalescent, colourless or slightly yellow solution.

PRESENTATION

FRAXIPARINE 0,2 ml, FRAXIPARINE 0,3 ml, FRAXIPARINE 0,4 ml:

Solution is filled in a clear ungraduated type I borosilicate glass cylinder of 1 ml capacity, with a stainless steel needle secured to the syringe body with a single component ultra violet polymerisable adhesive, with a chlorobutyl elastomer plunger with a polypropylene piston rod. The needle is covered with a transparent styrene butadiene copolymer safety device. The syringe is placed in a thermoformed, clear polyvinylchloride blister tray and is packed in a carton containing two or ten syringes.

FRAXIPARINE 0,6 ml, FRAXIPARINE 0,8 ml, FRAXIPARINE 1,0 ml:

Solution is filled in a clear graduated type I borosilicate glass cylinder of 1 ml capacity, with a stainless steel needle secured to the syringe body with a single component ultra violet polymerisable adhesive, with a chlorobutyl elastomer plunger with a polypropylene piston rod. The needle is covered with a transparent styrene butadiene copolymer safety device.

The syringe is placed in a thermoformed, clear polyvinylchloride blister tray and is packed in a carton containing two or ten syringes.

Not all strengths, packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep in original packaging until required for use.

Do not freeze.

Do not refrigerate, as the injection of cold solution may be painful.

Discard any unused portion of each syringe.

Do not mix with other preparations.

Do not use after the expiry date.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

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 1,0 ml: 31/8.2/0581

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Dates of registration:

FRAXIPARINE 0,2 ml: 11 October 2000

FRAXIPARINE 0,3 ml, FRAXIPARINE 0,4 ml, FRAXIPARINE 0,6 ml, FRAXIPARINE 0,8 ml: 10 October 2000

FRAXIPARINE 1,0 ml: 25 February 2000

Date of the most recent amendment to the professional information as approved by the Authority: 29 July 2002

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
1,0 ml	05/8.2/0019

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