Attachment 1: Product information for AusPAR Fraxiparine Aspen Pharmacare Australia Pty Ltd PM-2016-02215-1-3 Final 4 Sep 2018. This Product information was approved at the time this AusPAR was published.

FRAXIPARINE®

PRODUCT INFORMATION

NAME OF THE MEDICINE

Nadroparin calcium

DESCRIPTION

Fraxiparine is a sterile, clear preservative-free solution usually for subcutaneous injection containing nadroparin calcium 9,500 IU anti-Xa per 1.0 mL dissolved in water for injections.

Nadroparin is a low molecular weight heparin made by depolymerisation of standard heparin. It is a glycosaminoglycan with a mean molecular weight around 4,500 daltons. It possesses a high ratio of anti-Xa activity to anti-IIa activity between 2.5 to 4.0 compared to unfractionated heparin for which this ratio is one.

Anti-Xa denotes anti factor Xa activity. The ratio of anti-Xa to anti-IIa activity is 2.5 to 4.0.

One ICU is equivalent to 0.38 IU anti-Xa.

The excipients contained in the Fraxiparine solution are:
Calcium hydroxide solution or dilute hydrochloric acid (to adjust pH) and water for injections.

PHARMACOLOGY

Pharmacological Action

Nadroparin has both immediate and prolonged antithrombotic action.

Nadroparin exhibits a high-affinity binding to the plasma protein anti-thrombin III (ATIII). This binding leads to an accelerated inhibition of factor Xa and to a lesser extent, factor IIa (Anti-Xa:Anti-IIa ratio of 3.6:1), which contributes to the 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).

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

Pharmacokinetics

The pharmacokinetic properties of nadroparin have been assessed in plasma 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 6 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 is approximately 3.5 hours. However, in one study anti-Xa activity was detectable for at least 18 hours following a subcutaneous dose of 100 anti-Xa IC U/kg (38 anti-Xa IU/kg) in nine out of twelve study subjects.

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 and PRECAUTIONS).

Renal Impairment:

In patients with severe renal failure, a reduced dosage should be considered as elimination of anti-Xa activity is prolonged in such patients.

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, PRECAUTIONS).

CLINICAL TRIALS

A total of 6 published reports evaluating the safety and efficacy of nadroparin as a thromboprophylactic agent in hospitalised, acutely ill medical patients have been included to support the efficacy of this medicine. Five of the 6 safety and efficacy publications meet the NHMRC 1999 criteria of level 1 or level II evidence, providing sufficient details of study design, outcomes and statistical analysis for an independent assessment of the safety and efficacy of nadroparin in the proposed indication. The remaining safety and efficacy study was an uncontrolled prospective study

of acutely ill medical patients admitted to hospital, classified as low, intermediate or high risk of developing a venous thromboembolism (VTE).

The two systematic analyses both aimed to evaluate the efficacy and safety of low molecular weight heparins (LMWH), including nadroparin, when used as a thromboprophylactic agent in acutely ill medical patients with reduced mobility or bedridden. Both meta-analyses screened the design quality of individual studies prior to inclusion.

The first meta-analysis by Alikhan 2014 compared the safety and efficacy of either LMWH or unfractioned heparin (UFH) to placebo or no treatment, as well as LMWH to UFH. Of the three individual studies included in the analysis evaluating prophylactic nadroparin, one compared nadroparin to UFH, and the other to placebo. The third study compared nadroparin to placebo, however this study used a dose of nadroparin (7,500 anti-Xa IU) outside the dose range recommended and is supportive only.

The second meta-analysis by Dooley 2014 compared the safety and efficacy of various LMWH to either UFH or placebo. No individual study included in the analysis directly compared one LMWH to another, however an indirect analysis using common comparators was performed. Two of the individual trials compared nadroparin to UFH and two to placebo. One of the placebo comparisons used a dose of nadroparin (7,500 anti-Xa IU) which is outside the dose range recommended.

Both meta-analyses used the incidence of VTE as a primary efficacy outcome. Alikhan also reported the incidence of non fatal pulmonary embolism (PE) as a primary outcome, and Dooley, PE and mortality. Both analyses required deep vein thrombosis (DVT) to be objectively confirmed using imaging or venographic techniques. Both meta-analyses compared safety based on the incidence of major and minor bleeding, whilst Alikhan also evaluated the incidence of thrombocytopenia.

The overall conclusion from both meta-analyses was that patients treated with prophylactic LMWH generally were at a significantly lower risk of DVT, compared to those treated with UFH (OR 0.77; 95% CI 0.62 to 0.96; p=0.02), with no clear difference between LWMH and UFH with regards to the incidence of PE or death. In addition, patients treated with LMWH have a significantly lower risk of major bleeding (OR 0.43; 95% CI 0.22 to 0.83; p=0.01) and similar risk of developing thrombocytopenia.

In addition to the two meta-analyses, 4 individual clinical trial publications are included in this application, in support of the efficacy of nadroparin. Three of these trials are randomised controlled trials (RCT), while the remaining report summarises the outcome of an uncontrolled, prospective time series study. A total of 4,774 patients were administered nadroparin during these trials. The patients recruited into these trials were all over 40 years of age.

Two of the RCTs (Fraisse 2000 and Luba 2007) administered prophylactic nadroparin according to patient weight, consistent with the dosage recommendations (< 70 kg, 3800 anti-Xa IU and > 70 kg, 5700 anti-Xa IU).

Fraisse recruited 223 patients with acute, decompensated COPD requiring mechanical respiration. Patients with stroke and MI were excluded. Most patients (74%) exhibited at least one concomitant factor associated with an increased risk of thromboembolism, including chronic heart failure, venous insufficiency, obesity and cancer. The mean age of participants was 66.8 years in the nadroparin group and 69.4 years in the placebo control. The mean duration of treatment was 11 days. The primary efficacy outcome was the incidence of DVT. The safety criteria of this study included haemorrhage (major or minor) and severe thrombocytopenia.
High risk patients treated with nadroparin prophylaxis had a significantly lower (45%) incidence of DVT compared to placebo.

The overall incidence of adverse events reported by patients treated with nadroparin was not significantly different to placebo (46.3% versus 39.8%; p= 0.33).

Luba recruited 300 patients who were hospitalised for a medical condition, with an expected duration of immobility of at least 3 days. They were randomised to receive either short or long duration of nadroparin prophylaxis. The mean duration of nadroparin thromboprophylaxis in short duration group was 5.1 days and 14.5 days in longer duration group. The main reasons for immobilisation were severe respiratory disease, heart failure or stroke (91.6% of patients in total). Around 62% of participants were over 70 years of age. The primary efficacy outcome was the incidence of DVT. The safety was assessed based on the bleeding complications, thrombocytopenia, and local skin reactions. At the 3 month post treatment follow up, patients receiving longer courses of nadroparin recorded fewer (5) incidences of DVT compared to those receiving a short course (10).

The third RCT by Harenberg 1996 compared prophylactic nadroparin to low dose UFH in 1,968 medical patients aged 50-80 years, with an expected duration of bed rest and hospital stay >10 days and an indication for prophylaxis of thromboembolism. The LMWH group received nadroparin 0.3mL (3100 anti-Xa IU) and 2 placebo injections per day. The other group received calcium heparin 5000 IU three times a day. Treatment was administered every 8 hours for 10 days. The mean age of patients treated with nadroparin was 70.5 ± 8.3 years, with 57.5% being female. Patients had one or more risk factors for the development of thrombosis, such as obesity, varicoses, chronic venous insufficiency, post-thrombotic syndrome, oral contraception or estrogen, thrombocytosis or hyperviscosity syndrome, previous myocardial infarction, thrombotic cerebral infarction or peripheral arterial ischaemia. Overall, 15% of patients had experienced a previous stroke, 15% a previous myocardial infarction and 43% were diagnosed with some degree of cardiac insufficiency. The primary endpoints were proximal DVT of the lower limbs and/or PE, or asymptomatic proximal DVT detected by compression sonography. Four patients treated with UFH and 6 treated with nadroparin developed a DVT, demonstrating equivalence of treatments (p = 0.012).
The main safety endpoints were major and minor haemorrhage, other bleeding complications and a number of haematomas. The incidence of major and minor bleeding was no different between patients treated with nadroparin or UFH. There is some evidence that the incidence of thrombocytopenia may be less with nadroparin.
The incidence of injection site haematoma and erythema also appears to be lower for nadroparin compared to UFH
The dose of nadroparin (3100 anti-Xa IU) administered to the patients was lower than the dose recommended for this indication. Results showed that once daily nadroparin is as effective as UFH three times daily in preventing DVT and PE.

Based on a prospective observational study of almost 25,000 patients hospitalised for a range of acute medical conditions, Pottier 2000 estimated that, while the overall incidence of venous thrombosis in these patients was low, prophylactic nadroparin reduced the risk of venous thrombosis in high to moderate risk patients.

INDICATIONS

Prophylaxis against deep vein thrombosis (DVT) associated with general or orthopaedic surgery.
Treatment of DVT.
Prevention of clotting during haemodialysis.
Prophylaxis of venous thromboembolism in high-risk medical patients who are immobilised due to acute illness or hospitalised in an intensive care unit.

CONTRAINDICATIONS

Fraxiparine is contraindicated in patients:

- hypersensitive to nadroparin, or any of the excipients of nadroparin injections.
- with a history of thrombocytopenia with nadroparin (see PRECAUTIONS).
- with an increased risk of haemorrhage including those with bleeding disorders (except for disseminated intravascular coagulation not induced by heparin).
- with active bleeding or organic lesions likely to bleed (such as active peptic ulceration), haemorrhagic cerebrovascular accident or infective endocarditis.
- with severe renal failure (creatinine clearance<30 mL/min) receiving treatment for DVT.

PRECAUTIONS

Nadroparin is not indicated for the treatment of unstable angina or myocardial infarction.

Heparin Induced Thrombocytopenia:

Because of the possibility of heparin induced thrombocytopenia, **regular monitoring of platelet count is recommended throughout the course of treatment with Fraxiparine.**

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
- worsening of the initial thrombosis while on therapy
- thrombosis occurring on treatment
- disseminated intravascular coagulation.

In this event, Fraxiparine 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 (LMWH)), treatment with Fraxiparine 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 LMWH), substitution with a different anti-thrombotic 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.

Increased Risk of Bleeding:

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/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. 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).

A dose reduction is required for patients with severe renal impairment (creatinine clearance less than 30 mL/min) receiving prophylactic treatment of DVT (see DOSAGE AND ADMINISTRATION) and Fraxiparine is contraindicated in patients with severe renal impairment receiving treatment for DVT (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 taking drugs that may cause hyperkalaemia [eg. Angiotensin-converting (ACE) Inhibitors, Nonsteroidal anti-inflammatory drugs (NSAIDs)].

The risk of hyperkalaemia appears to increase with duration of therapy, but is usually reversible.

Plasma potassium should be monitored in patients at risk.

Spinal/epidural haematomas:

The risk of spinal/epidural haematomas is increased by indwelling epidural catheters or by 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 central nervous blockade or spinal puncture and of an anti-coagulant therapy should be decided only after careful individual benefit/risk assessment in the following situations:

- in patients already treated with anticoagulant therapy, the benefits of central nervous blockade or spinal puncture must be carefully balanced against the risks.
- in patients planned to undergo elective surgery with central nervous blockade or spinal puncture, 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 Fraxiparine 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.

Where concomitant prescription of central nervous blockade or spinal puncture and LMWH is used, patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

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*.*

THE LOW MOLECULAR WEIGHT HEPARINS ARE CLINICALLY NOT INTERCHANGEABLE AS THEY DIFFER FROM ONE ANOTHER IN HAVING DIFFERENT MOLECULAR WEIGHT PROFILES, DIFFERENT SPECIFIC ACTIVITIES (ANTI Xa TO ANTI IIa ACTIVITIES), DIFFERENT RATE OF PLASMA CLEARANCE, DIFFERENT DOSAGE REGIME ETC.

Effects on Fertility:

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

Nadroparin at subcutaneous doses up to 40 mg/kg (approximately 3,800 anti-Xa IU/kg) did not affect the fertility or reproductive performance of male and female rats.

Use in Pregnancy:

Category C

In animal studies, nadroparin did not cause teratogenic or embryotoxic effects when administered to pregnant rats and rabbits at subcutaneous doses up to 3,800 anti-Xa IU/kg/day. A study in rats showed that only minimal amounts of radiolabelled nadroparin calcium were able to cross the placental barrier (0.002% of applied dose per foetus). However, there is only limited clinical data concerning transplacental passage of nadroparin in pregnant women. Therefore, the use of

Fraxiparine during pregnancy is not advised, unless the therapeutic benefits outweigh the possible risks. An increased incidence of foetal loss and prematurity may be associated with maternal haemorrhage.

Use in Lactation:

A study with radiolabelled nadroparin calcium at 2.5 mg/kg/day (230 anti-Xa IU/kg/day) in lactating rats has shown that drug-related material is excreted in milk with about the same concentration in the milk as in maternal plasma. There is limited information on the excretion of nadroparin in breast milk. Therefore, the use of Fraxiparine during breast feeding is not advised.

Use in the Elderly:

Elderly patients and patients with renal insufficiency may show delayed elimination of nadroparin calcium. It is recommended that renal function is assessed before initiating treatment. Reduced doses should be considered.

Genotoxicity

Preclinical data has revealed no special hazard based on conventional studies of genotoxicity.

Carcinogenicity

Nadroparin calcium has not been tested in long-term animal studies of carcinogenic potential.

Ability to perform tasks that require judgement, motor or cognitive skills:

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

INTERACTIONS WITH OTHER MEDICINES

Combined therapy with the following drugs is not recommended:

In the prophylaxis against deep vein thrombosis (DVT) associated with general or orthopaedic surgery, treatment of DVT and in the prevention of clotting during haemodialysis, the concomitant use of aspirin, other salicylates, NSAIDs, ticlopidine and other 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.

Combinations requiring caution:

Fraxiparine 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 Fraxiparine should be continued until the International Normalisation Ratio (INR) is stabilised at the target value. Careful clinical and biological monitoring should be undertaken.

ADVERSE EFFECTS

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 WITH OTHER MEDICINES).

Rare: Thrombocytopenia (including heparin-induced thrombocytopenia*)* (see PRECAUTIONS), thrombocytosis.

Very rare: Eosinophilia, reversible following treatment discontinuation.

Immune system disorders

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

Hypersensitivity reactions sometimes require discontinuation of treatment.

Metabolism and nutrition disorders

Very rare: Reversible hyperkalaemia related to heparin-induced aldosterone suppression, particularly in patients at risk (see 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 (see PRECAUTIONS) usually occurring at the injection site.

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.

Adverse Events by System Organ Class reported in studies conducted in immobilised medical patients.

The following adverse events were reported in three RCT which evaluated the safety of nadroparin when administered as a thrombo-prophylactic agent in immobilised medical patients.

Study	**Fraisse 2000 N(%)**		**Harenberg 1996 N(%)**		**Forette 1995 N(%)**	
Body System	Nadroparin (n=108)	Placebo (n=113)	Nadroparin (n=810)	Heparin (n=780)	Nadroparin (n=146)	Heparin (n=149)
Blood & lymphatic system disorders						
Decreased haemoglobin	17(15.7%)	14(12.4%)	-	-	-	-
Decreased platelets	10(9.3%)	7(6.2%)	-	-	-	-
Cardiac disorders						
Atrial fibrillation	-	-	0	1(0.13)	-	-
Cardiac insufficiency	-	-	9(1.1)	1(0.13)	-	-
Myocardial infarction	-	-	1(0.13)	0	-	-
Stroke	-	-	4(0.5)	0	-	-
Cardiogenic shock	-	1(0.9)			-	-
Infections & infestations						
Septic shock	5(4.6)	3(2.6)	-	-	-	-
Investigations						
Elevated liver enzymes	-	-	7(0.9)	21(2.7)	-	-
Metabolic & nutritional disorders						
Diabetes	-	-	1(0.12)	-	-	-
Neoplasms benign & malignant						
Carcinoma	-	-	4(0.5)	3(0.4)	-	-
Renal & urinary disorders						
Haematuria	1(0.9)	-	-	-	-	-
Respiratory, thoracic & mediastinal disorders						
Chronic obstructive lung	-	-	0	1(0.13)	-	-

Study	**Fraisse 2000 N(%)**		**Harenberg 1996 N(%)**		**Forette 1995 N(%)**	
Body System	Nadroparin (n=108)	Placebo (n=113)	Nadroparin (n=810)	Heparin (n=780)	Nadroparin (n=146)	Heparin (n=149)
disease						
Pneumonia	-	-	4(0.5)	1(0.13)	-	-
Skin & subcutaneous tissue disorders						
Local erythema	-	-	33(4)	56(7)	-	-
Local allergy	-	-	8(1)	16(2)	-	-
Vascular disorders						
Haemorrhage	25(23)	18(16)	-	-	-	-
Major bleed	6(5)	3(2)	5(0.6)	4(0.5)	0	4(2.7)
Minor bleed	19(18)	15(13)	3(0.4)	7(0.9)	2(1.4)	5(3.3)
Thrombocytopenia	10(9)	7(6)	0	4(0.5)	-	-
Haematoma	-	-	-	-	16(11)	41(27.5)
Deep vein thrombosis	0	1(0.9)	-	-	3(2)	4(2.7)
Pulmonary embolism	-	-	1(0.12)	-	0	1(0.7)
Ischaemic vascular event	1(0.9)	-	-	-	-	-

DOSAGE AND ADMINISTRATION

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

Platelet count must be monitored throughout treatment with Fraxiparine (see PRECAUTIONS). Specific recommendations regarding the timing of Fraxiparine dosing surrounding spinal/epidural anaesthesia or spinal lumbar puncture should be followed (see PRECAUTIONS).

Administration

Usually by subcutaneous injection into the lateral abdominal wall.

When Fraxiparine is given 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 intramuscular administration.

Removal of Packaging Prior to Injection

To divide the syringes, carefully fold, several times, the twin pack 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 backing film completely from the plastic tray (starting from the plunger end), then allow the syringe to roll onto the palm of your other hand.

The rubber cap over 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 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 - this may bend the needle.

Fraxiparine 0.2 mL - 1,900 IU anti-Xa, 0.3 mL - 2,850 IU anti-Xa and 0.4 mL - 3,800 IU anti-Xa prefilled 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 anti-Xa, 0.8 mL - 7,600 IU anti-Xa and 1.0 mL - 9,500 IU anti-Xa prefilled 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.

2. Pinch a skin fold.
   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. There may be a small air bubble in the barrel of the syringe, but this does not have to be removed.

4. Still holding the skin fold, withdraw the needle vertically.
   Do not rub the site of injection.

5. After the injection is given, install the safety system on the Fraxiparine syringe and dispose of carefully.

Fraxiparine is not intended for intramuscular or intravenous administration (except in haemodialysis)

Dosage

Fraxiparine should only be administered by subcutaneous route (except in haemodialysis).

Prophylaxis of DVT:

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
40-60	0.2	1,900	0.3	2,850
61-80	0.3	2,850	0.4	3,800
81-124	0.4	3,800	0.6	5,700

Treatment of DVT:

In the treatment of DVT, oral anticoagulant therapy should be initiated as soon as possible unless contraindicated. Treatment with Fraxiparine should not be stopped before the target International Normalised Ratio (INR) is reached.

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

Prevention of Clotting During Haemodialysis:

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

An additional smaller dose may be given during dialysis for sessions lasting longer than 4 hours. The dose in subsequent dialysis sessions should be adjusted as necessary according to observed effect.

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

Fraxiparine is contraindicated in patients with an increased risk of haemorrhage (see CONTRAINDICATIONS).

Medical Patients immobilised due to acute illness:

Fraxiparine is administered subcutaneously once daily. Treatment should be started within 12-24 hours of admission and should only be initiated when expected duration of bedrest/immobilisation is at least 3 days. Maximum duration of treatment is 28 days.

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.

Dosage for the Elderly

No dosage adjustment is necessary in the elderly, unless renal function in impaired. It is recommended that renal function is assessed before initiating treatment (see Dosage for the Renally Impaired below and Pharmacokinetics).

Dosage for the Renally Impaired

The following dose reduction recommendations are based on population pharmacokinetic modelling and the efficacy and safety of the dose reductions have not been evaluated in clinical trials.

Prophylactic treatment of DVT:

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%.

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

Treatment of DVT:

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%.

However, Fraxiparine is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS, PRECAUTIONS and Pharmacokinetics).

Children and Adolescents

Fraxiparine 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.

Hepatic impairment

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

OVERDOSAGE

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 Fraxiparine is usually sufficient.

Treatment

There is no clinical experience on the use of protamine sulphate to neutralise the effect of nadroparin overdosage. It should be considered only in emergency situations. Serious overdosage may be partly neutralised by the slow intravenous injection of protamine. Particular care should be taken to avoid overdosage with protamine as even with high doses of protamine, the anti Xa activity of Fraxiparine may remain, even though the anticoagulant activity is neutralised. 6 mg of protamine sulphate neutralises about 0.1 mL (950 IU AXa) Fraxiparine. The amount of protamine to be injected should take into account the time elapsed from the injection of Fraxiparine and a reduction may be appropriate. If transfusion is required, fresh frozen plasma should be used.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Disposable glass pre-filled single use syringes containing nadroparin calcium 9,500 IU anti-Xa/mL in water for injections with sufficient calcium hydroxide or dilute hydrochloric acid to adjust the pH to between 5 and 7.5.

Volume	Type of Syringe	Nadroparin Calcium (IU anti-Xa)	Pack size
0.2 mL	Ungraduated	1,900	2 and 10
0.3 mL	Ungraduated	2,850	2 and 10
0.4 mL	Ungraduated	3,800	2 and 10
0.6 mL	Graduated	5,700	2 and 10
0.8 mL	Graduated	7,600	2 and 10
1.0 mL	Graduated	9,500	2 and 10

* All volumes and pack sizes may not be available in Australia.

Store below 25°C but do not freeze. Do not refrigerate as cold injections may be painful.

Use once only and discard any unused portion of each syringe. Do not mix with other preparations. Do not use after the expiry date shown on the carton.

NAME AND ADDRESS OF THE SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065

POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG):

14 August 1995

DATE OF MOST RECENT AMENDMENT:

31 August 2017

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