NEW ZEALAND DATA SHEET

1. CRUSIA-AFT AND CRUSIA-AFT FORTE

Crusia-AFT 100 mg/mL solution for injection
Crusia-AFT Forte 150 mg/mL solution for injection.

Crusia-AFT and Crusia-AFT Forte are biosimilar medicines.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Crusia-AFT 100 mg/mL solution for injection:
Each 0.2 mL prefilled syringe contains 20 mg (anti-Xa: 2,000 IU) enoxaparin sodium.
Each 0.4 mL prefilled syringe contains 40 mg (anti-Xa: 4,000 IU) enoxaparin sodium.
Each 0.6 mL prefilled syringe contains 60 mg (anti-Xa: 6,000 IU) enoxaparin sodium.
Each 0.8 mL prefilled syringe contains 80 mg (anti-Xa: 8,000 IU) enoxaparin sodium.
Each 1 mL prefilled syringe contains 100 mg (anti-Xa: 10,000 IU) enoxaparin sodium.

Crusia-AFT Forte 150 mg/mL solution for injection:
Each 0.8 mL prefilled syringe contains 120 mg (anti-Xa: 12,000 IU) enoxaparin sodium.
Each 1 mL prefilled syringe contains 150 mg (anti-Xa: 15,000 IU) enoxaparin sodium.

Enoxaparin sodium is a biological substance obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa.

For the full list of excipients, see section 6.1.

Crusia-AFT* is a biosimilar medicine. The prescribing physician should be involved in any decision regarding interchangeability with other products. Additional information is available on the following website (http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp). Data comparing Crusia-AFT to Clexane can be found in section 5.1 of this datasheet.

*Any subsequent reference to Crusia-AFT refers to both Crusia-AFT and Crusia-AFT Forte.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Crusia-AFT is indicated in adults for:

- Prophylaxis of venous thromboembolic disease, in particular those which may be associated with orthopaedic, general, major colorectal or cancer surgery.
- Prophylaxis of venous thromboembolism in general medical patients bedridden due to acute illnesses including acute heart failure, respiratory failure, severe infections, rheumatic disease.
- Treatment of venous thromboembolic disease.
- Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
- Prevention of thrombus formation in the extra-corporeal circulation during haemodialysis.
- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

4.2 Dose and method of administration

LMWH PRODUCTS ARE NOT CLINICALLY INTERCHANGEABLE.
They differ in their manufacturing process, molecular weights, specific anti-Xa activities, units and dosage. The biological activity of different LMWHs cannot be expressed in a test allowing for a simple dose comparison. Different low molecular weight heparins may not be bioequivalent in terms of their labelled anti-Xa activities and alternative products should not be introduced nor interchanged during a course of treatment.

Not to be administered by the intramuscular route.
For subcutaneous use: do not mix Crusia-AFT with other injections or solutions.
For intravenous use: see section 4.2, 'Dose: Treatment of acute ST-segment elevation myocardial infarction (STEMI)'.

Dose

Prophylaxis of venous thrombosis in surgical patients

Prophylaxis against thromboembolism should be tailored according to the patient's risk. Risk factors include age over 40 years, history of deep vein thrombosis or pulmonary embolism, surgery and other trauma, prolonged immobilisation, cardiac disease, obesity, malignancy, varicose veins, hypercoagulable states, pregnancy and the puerperium, oral contraceptives, severe infection, inflammatory bowel disease.

a) High risk patients

In patients with high risk of thromboembolism, a dosage of 40 mg (0.4 mL; anti-Xa: 4000 IU) should be administered subcutaneously once daily. In high risk patients undergoing surgery, the initial dose should be given approximately 12 hours preoperatively or 12 hours postoperatively. The timing of the first dose may need to be modified if spinal/epidural anaesthesia is to be performed (see section 4.4, 'Spinal/epidural anaesthesia').

Prophylaxis should be continued at 40 mg once daily for 7 to 10 days or until the risk of thromboembolism has diminished.

b) Moderate risk patients

In patients with a moderate risk of thromboembolism, the recommended dosage is 20 mg (0.2 mL; anti-Xa: 2000 IU) subcutaneously once daily. In moderate risk patients undergoing surgery, the initial dose should be given approximately 2 hours preoperatively. The timing of the first dose may need to be modified if spinal/epidural anaesthesia is to be performed (see section 4.4, 'Spinal/epidural anaesthesia').

Duration of therapy

High to moderate risk: Prophylaxis should be continued at 20 mg once daily for 7 to 10 days or until the risk of thromboembolism has diminished.

Prolonged thromboprophylaxis

Therapy with 40 mg once daily for 30 post-operative days has been proven to be beneficial in total hip replacement surgery.

Under normal conditions of use, enoxaparin does not modify global clotting tests and therefore there is no need to perform these tests in order to monitor therapy.

Prophylaxis of venous thromboembolism in medical patients

The recommended dose of Crusia-AFT is 40 mg once daily by subcutaneous injection.

Treatment with Crusia-AFT is prescribed for a minimum of 6 days and continued until the return to full ambulation, for a maximum of 14 days.

Treatment of venous thrombosis

The initial clinical trials which established the efficacy of enoxaparin (Clexane) in the treatment of deep venous thrombosis were conducted on patients who were initially treated with heparin and then changed to Clexane when a definitive diagnosis was established. However, the use of heparin prior to enoxaparin is not currently recommended. The average duration of therapy in the clinical trials was 10 days. No data are available on the safety of long term treatment. Data on use in patients over 65 years of age in these trials were limited.

The recommended dosage for treatment of established deep vein thrombosis with Crusia-AFT is 1.5 mg/kg body weight once daily (150 IU anti-Xa activity/kg body weight) or 1 mg/kg body weight (100 IU anti-Xa activity/kg bodyweight) twice daily subcutaneously. In high risk patients, e.g., the obese or patients with baseline iliac vein thrombosis or cancer, a dose of 1 mg/kg body weight administered twice daily may be more beneficial.

Warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of commencing enoxaparin initiation). Crusia-AFT should be continued for a minimum of 5 days and until a

therapeutic anticoagulant effect has been achieved (International Normalisation Ratio 2.0 to 3.0).

Treatment of unstable angina and non-Q-wave myocardial infarction
The recommended dose of Crusia-AFT is 1 mg/kg (100 IU anti-Xa activity/kg) every 12 hours by subcutaneous injection, administered concurrently with oral aspirin (100 to 300 mg once daily).

Treatment with Crusia-AFT in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilisation. The usual duration of treatment is 2 to 8 days.

Treatment of acute ST-segment elevation myocardial infarction (STEMI)
In patients with acute ST-segment elevation myocardial infarction, administered in conjunction with a fibrinolytic (fibrin-specific or non-fibrin specific), the recommended dose of Crusia-AFT is a single IV bolus of 30 mg plus a 1 mg/kg SC dose, followed by 1 mg/kg administered SC every 12 hours (maximum 100 mg for each of the first two SC doses only, followed by 1 mg/kg dosing for the remaining doses). For dosage in patients ≥75 years of age, see section 4.2, 'Elderly' and 'Renal impairment'.

When administered in conjunction with a thrombolytic (fibrin-specific or non-fibrin specific), Crusia-AFT should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. All patients should receive aspirin as soon as they are identified as having STEMI (100 to 300 mg once daily, unless contraindicated). The recommended duration of Crusia-AFT treatment is 8 days or until hospital discharge, whichever comes first.

For patients managed with Percutaneous Coronary Intervention (PCI): If the last Crusia-AFT SC administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last Crusia-AFT SC administration was given more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of Crusia-AFT should be administered (see section 4.4, 'Percutaneous coronary revascularisation procedures').

Haemodialysis
In patients undergoing repeated sessions of haemodialysis, the prevention of thrombosis in the extracorporeal blood circuit is obtained by injection of a dose of 1 mg/kg (100 IU anti-Xa activity/kg) into the arterial line of the dialysis circuit at the start of the session. The dose is usually sufficient for a 4 hour haemodialysis session. If fibrin rings are formed, a further dose of 0.5 to 1 mg/kg (50 to 100 IU anti-Xa activity/kg) should be made depending on the time before the end of the dialysis.

In haemodialysed patients with a high risk of haemorrhage, (in particular, in pre or post-operative dialysed patients) or with a progressive haemorrhagic disorder, the dialysis sessions may be carried out by using a dose of 0.5 mg/kg (50 IU anti-Xa activity/kg) (double vascular access) or 0.75 mg/kg (75 IU anti-Xa activity/kg) (single vascular access).

Renal impairment

Severe renal impairment

A dosage adjustment is required for patients with severe renal impairment (creatinine clearance <30 mL/min), according to the following tables.

The following dosage adjustments are recommended for the treatment dosage ranges.

Standard dosing	Severe renal impairment
1 mg/kg SC twice daily	1 mg/kg SC once daily
1.5 mg/kg SC once daily	1 mg/kg SC once daily
Acute STEMI patients < 75 years of age	
30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC twice daily (Max 100 mg for each of the first two SC doses)	30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC once daily (Max 100 mg for first SC dose only)
Acute STEMI patients ≥ 75 years of age	
0.75 mg/kg SC twice daily without initial bolus (Max 75 mg for each of the first two SC doses)	1 mg/kg SC once daily without initial bolus (Max 75 mg for first SC dose only)

The following dosage adjustments are recommended for the prophylactic dosage ranges.

Standard dosing	Severe renal impairment
40 mg SC once daily	20 mg SC once daily
20 mg SC once daily	20 mg SC once daily

The recommended dosage adjustments do not apply to the haemodialysis indication.

Moderate and mild renal impairment

Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, careful clinical monitoring is advised.

Hepatic impairment

In the absence of clinical studies, caution should be used in hepatically-impaired patients.

Elderly

For treatment of acute ST-segment elevation myocardial infarction in elderly patients ≥75 years of age, do not use an initial IV bolus. Initiate dosing with 0.75 mg/kg SC every 12 hours (maximum 75 mg for each of the first two SC doses only, followed by 0.75 mg/kg dosing for the remaining doses).

No dose reduction is necessary in the elderly for other indications, unless kidney function is impaired; however clinical observation is advised (see section 4.4, 'Renal impairment' and 'Use in the elderly').

Paediatric population
The safety and efficacy of Crusia-AFT in children have not been established.

Method of administration
Subcutaneous or intravenous (for the treatment of acute STEMI only, see section 4.2, 'Dose').
Crusia-AFT should not be administered by the intramuscular route.

Subcutaneous injection technique
Injection should be made preferably when the patient is reclining. Crusia-AFT is administered by deep subcutaneous injection. Injection of Crusia-AFT should be alternated between the left and right anterolateral abdominal wall using a different site for each injection. Do not expel the air bubble from the syringe before the injection to avoid the loss of drug. Crusia-AFT contains no antimicrobial agent and should be used only once and then discarded.

The needles on the prefilled syringes of Crusia-AFT are covered in a silicon coating, to enable ease of penetration. Do not wipe the needle or allow Crusia-AFT solution to crystallise on the needle prior to use, as this will damage the silicon coating. A "dart" injection technique should be used to administer Crusia-AFT. Do not rub the injection site after administration.

Intravenous (bolus) injection technique (for the treatment of acute STEMI)
For intravenous injection, Crusia-AFT should be administered through an intravenous line and should not be co-administered with other medications. To avoid the possible mixture of Crusia-AFT with other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of Crusia-AFT to clear the port of drug. Crusia-AFT may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

Prefilled syringes
The prefilled disposable syringe is ready for immediate use. The whole length of the needle should be introduced vertically (at a 90° angle to the skin) into a skin fold gently held between the thumb and forefinger. The skin fold should be held throughout the duration of the injection.

Graduated prefilled syringes
When using the 60 mg, 80 mg, 100 mg, 120 mg and 150 mg graduated prefilled syringes, the volume to be injected should be measured precisely according to the dosage recommended, without expelling the air bubble while adjusting dosage. If the dose required is exactly 60, 80, 100, 120 or 150 mg, inject the full contents of the syringe. The whole length of the needle should be introduced vertically (at a 90° angle to the skin) into a skin fold gently held between the thumb and forefinger. The skin fold should be held throughout the duration of the injection.

4.3 Contraindications

Enoxaparin sodium is contraindicated in patients with:

- Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including other low molecular weight heparins (LMWHs), or to any of the excipients listed in section 6.1.
- Acute bacterial endocarditis.
- Conditions with a high risk of uncontrolled haemorrhage including major bleeding disorders, focal lesions, haemorrhagic stroke, active ulcerative conditions showing a tendency to haemorrhage (e.g. peptic ulcer, ulcerative colitis).
- History of immune-mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (see section 4.4).

4.4 Special warnings and precautions for use

LMWH PRODUCTS ARE NOT CLINICALLY INTERCHANGEABLE.

They differ in their manufacturing process, molecular weights, specific anti-Xa activities, units and dosage. The biological activity of different LMWHs cannot be expressed in a test allowing for a simple dose comparison. Different low molecular weight heparins may not be bioequivalent in terms of their labelled anti-Xa activities and alternative products should not be introduced nor interchanged during a course of treatment.

Not to be administered by the intramuscular route.

Risk of haemorrhage

Crusia-AFT should be used with extreme caution in conditions with increased risk of haemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, haemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors. Major haemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal. As with other anticoagulants, bleeding can occur at any site during therapy with Crusia-AFT (see section 4.8). An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site and appropriate treatment instituted.

Concomitant medical conditions

Crusia-AFT should be used with caution in patients with the following conditions: hepatic insufficiency, a bleeding diathesis, uncontrolled arterial hypertension, a history of gastrointestinal ulceration, impaired haemostasis, recent ischaemic stroke, diabetic retinopathy, recent neuro- or ophthalmologic surgery and haemorrhage.

Heparin-induced thrombocytopenia (HIT)

Use of enoxaparin sodium in patients with a history of immune-mediated HIT within the past 100 days or in the presence of circulating antibodies is contraindicated (see section 4.3). Circulating antibodies may persist for several years.

Crusia-AFT is to be used with extreme caution in patients with a history (more than 100 days) of heparin-induced (including low molecular weight heparins) thrombocytopenia without circulating antibodies. The decision to use Crusia-AFT in such a case must be made only after a careful benefit risk assessment and after non-heparin alternative treatments are considered.

Spinal/epidural anaesthesia

There have been rare cases of neuraxial haematomas reported with the concurrent use of enoxaparin and spinal/epidural anaesthesia resulting in long-term or permanent paralysis. These events are rare with enoxaparin dosage regimens 40 mg once daily or lower. The risk is greater with higher enoxaparin dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs) (see section 4.5). The risk also appears to be increased by traumatic or repeated neuraxial puncture or in patients with a history of spinal surgery or spinal deformity.

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin and epidural or spinal anaesthesia/analgesia, the pharmacokinetic profile of the drug should be considered (see section 5.2). Placement and removal of the needle/catheter is best performed when the anticoagulant effect of enoxaparin is low.

Placement or removal of an epidural or spinal needle or catheter should be delayed for at least 12 hours after administration of lower doses (20 mg once daily, 30 mg once or twice daily or 40 mg once daily) of enoxaparin, and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or 1.5 mg/kg once daily) of enoxaparin. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial haematoma will be avoided. Patients receiving the 0.75 mg/kg twice-daily dose or the 1 mg/kg twice-daily dose should not receive the second enoxaparin dose in the twice-daily regimen to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing of a subsequent enoxaparin dose after catheter removal cannot be made, consider delaying this next dose for at least four hours, based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine clearance <30 mL/minute, additional considerations are necessary because elimination of enoxaparin is more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day).The patient's regular enoxaparin dose may need to be delayed to ensure this. If blood is present during needle/catheter placement, the subsequent dose of enoxaparin should be delayed for 24 hours after placement.

Should the physician decide to administer anticoagulation in the context of epidural/spinal anaesthesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of spinal haematoma such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Patients should be instructed to inform their physician immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal

haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

Thrombocytopenia

Thrombocytopenia can occur with the administration of enoxaparin. Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 1.3% in patients given enoxaparin, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials. Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given enoxaparin, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, enoxaparin should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

Prosthetic heart valves

There have been no adequate studies to assess the safe and effective use of enoxaparin in preventing thromboembolism in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Confounding factors, including underlying disease and insufficient clinical data, limit the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and foetal death. Pregnant women with mechanical prosthetic heart valves may be at a higher risk for thromboembolism. The use of enoxaparin cannot be recommended for this purpose (see section 4.6).

Percutaneous coronary revascularisation procedures

To minimise the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non Q-wave myocardial infarction and ST-segment elevation acute myocardial infarction, adhere precisely to the intervals recommended between enoxaparin doses. It is important to achieve haemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, the sheath should be removed 6 hours after the last IV/SC enoxaparin injection. If the treatment with enoxaparin is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or haematoma formation.

Renal impairment

In patients with renal impairment, there is an increase in exposure of enoxaparin which increases the risk of bleeding. Since exposure of enoxaparin is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, careful clinical observation is advised (see section 4.2, 'Renal impairment').

Pharmacokinetics of enoxaparin are altered in renal impairment (see section 5.2). The extent to which

a defect in platelet function in severe renal failure might further contribute to bleeding risk is unknown.

Hepatic impairment
See section 4.2.

Low weight
An increase in exposure of enoxaparin with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical observation is advised in these patients.

Obese patients
Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m^2) have not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

Paediatric use
The safety and efficacy of Crusia-AFT in children have not been established.

Use in the elderly
No increased bleeding tendency is observed in the elderly with the prophylactic dosage ranges. Elderly patients (especially patients eighty years of age and older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges. Careful clinical observation is advised. A dosage adjustment may be necessary in elderly patients due to age-related impairment of renal function (see section 4.2, 'Renal impairment').

In the clinical study for treatment of acute STEMI, in patients ≥75 years of age (n = 2532) the rate of death or myocardial re-infarction was higher than in the global population but lower in the enoxaparin group (24.8%) than in the UFH group (26.3%, relative risk 0.94, p = 0.38). Patients ≥75 years of age did not receive a 30 mg IV bolus prior to the normal dosage regimen and had their SC dose adjusted to 0.75 mg/kg every 12 hours (see section 4.2).

In patients ≥75 years of age, the rate of TIMI major bleeding was higher than in the global population and was higher in the enoxaparin group (3.3%) for patients ≥75 years of age compared with the UFH group (2.9%, RR 1.15, p = 0.57).

Compared to younger patients (<65 years), the rate of TIMI major bleeding was higher in patients >65 years of age (respectively 1.2% and 2.5%) and was higher in the enoxaparin group as compared to the UFH group (see section 5.1).

Effect on laboratory tests
At doses used for prophylaxis of venous thromboembolism, enoxaparin does not influence bleeding time and global blood coagulation tests significantly, nor does it affect platelet aggregation or binding of fibrinogen to platelets.

At higher doses, increases in aPTT and ACT (activated clotting time) may occur. Increases in aPTT and ACT are not linearly correlated with increasing enoxaparin antithrombotic activity and therefore are unsuitable and unreliable for monitoring enoxaparin activity.

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with enoxaparin. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of enoxaparin activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of enoxaparin in patients with significant renal impairment. If during enoxaparin therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of enoxaparin.

Monitoring of platelet counts

The risk of antibody-mediated heparin-induced thrombocytopenia also exists with LMWHs. Should thrombocytopenia occur, it usually appears between the 5th and 21st day following the beginning of enoxaparin treatment. Therefore, it is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin and then regularly thereafter during the treatment. In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50% of the initial value), enoxaparin treatment must be immediately discontinued and the patient switched to another therapy.

4.5 Interaction with other medicines and other forms of interaction

Clinical trials revealed no adverse effects that could be caused by drug interactions including no pharmacokinetic interactions between enoxaparin and thrombolytics when administered concurrently.

It is recommended that agents which affect haemostasis should be discontinued prior to enoxaparin therapy unless strictly indicated. These agents include medications such as: anti-coagulants, thrombolytics, non-steroidal anti-inflammatory agents (including ketorolac), preparations containing aspirin, systemic salicylates, ticlopidine, dextran 40, clopidogrel, other anti-platelet agents including glycoprotein IIb/IIIa antagonists or systemic glucocorticoids. If the combination is indicated, enoxaparin should be used with careful clinical and laboratory monitoring of the haemostatic factors, when appropriate.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C.

In humans, there is no evidence that enoxaparin sodium crosses the placental barrier during the second trimester of pregnancy. There is no information available concerning the use of enoxaparin during the first and the third trimesters. As there are no adequate and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this medicine should be used

during pregnancy only if the physician has established a clear need.

Animal studies have not shown any evidence of teratogenicity (see section 5.3).

There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.

There have been post-marketing reports of foetal death when pregnant women received enoxaparin. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk of bleeding. Haemorrhage can occur at any site and may lead to death of mother and/or foetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the foetus and the mother if enoxaparin is administered during pregnancy.

The use of enoxaparin for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and foetal death. There have been isolated post-marketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at a higher risk for thromboembolism. In the absence of additional dosing, efficacy and safety information in this circumstance, enoxaparin is not recommended for use in pregnant women with mechanical prosthetic heart valves (see section 4.4, 'Prosthetic heart valves').

Breastfeeding

It is unknown whether enoxaparin is excreted into the breast milk of humans. In lactating rats, the concentration of ^{35}S-enoxaparin sodium or its labelled metabolites in milk was similar to that in maternal plasma. Apart from lower birth weights and slightly delayed physical development, there were no significant adverse effects of 20 mg/kg/day enoxaparin SC in a peri- and post-natal study in rats. Effects of enoxaparin on lactating women have not been studied. As a precaution, women should be advised not to breast feed while using enoxaparin.

Fertility

Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day.

4.7 Effects on ability to drive and use machines

Crusia-AFT has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Enoxaparin sodium has been evaluated in more than 15,000 patients. The following information relates to adverse events observed in controlled clinical trials with patients given enoxaparin (Clexane) for prophylaxis of deep vein thrombosis following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications (n = 1176), prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility (n = 1169), treatment of deep vein thrombosis with or without pulmonary embolism (n = 669) or with patients given enoxaparin for the treatment of unstable angina or non-Q-wave myocardial infarction, administered concurrently with aspirin (n = 1578) or with patients given enoxaparin for the treatment of acute ST-segment elevation myocardial infarction (n = 10176).

In clinical studies, haemorrhages, thrombocytopenia and thrombocytosis were the most commonly reported reactions (see section 4.4 and 'Description of selected adverse reactions' below).

b. Tabulated list of adverse reactions

Events observed following the marketing of enoxaparin sold as Clexane are included in the following list. Voluntary reports of adverse events that have been received since market introduction (without causal relationship) that are not listed previously are also cited below. Reactions reported from post-marketing experience are indicated by *.

Reported adverse events are presented at frequencies of:

Very common	> 1/10 (10%)
Common	≥ 1/100 (1%) and < 1/10 (10%)
Uncommon	≥ 1/1000 (0.1%) and < 1/100 (1%)
Rare	≥ 1/10000 (0.01%) and < 1/1000 (0.1%)
Very rare	< 1/10000 (<0.01%)
Frequency not known	Not known (cannot be estimated from the available data)

Blood and the lymphatic symptom disorders

Common:	Haemorrhage, anaemia, thrombocytopenia, thrombocytosis
Rare:	Immuno-allergic thrombocytopenia with or without thrombosis*; in some of them, thrombosis was complicated by organ infarction or limb ischaemia (see section 4.4).
Frequency not known:	Asymptomatic and reversible increases in platelet counts*, haemorrhagic anaemia*, eosinophilia*

Vascular disorders

Rare:	Spinal or neuraxial haematomas with the concurrent use of enoxaparin and spinal/epidural anaesthesia, spinal puncture or post-operative indwelling catheters*. These events have resulted in varying degrees of neurologic injuries including long- term or permanent paralysis (see section 4.4).

Immune system disorders

Common:	Allergic reaction
Rare:	Anaphylactic/anaphylactoid reaction, including shock*
	Cutaneous (bullous) or systemic allergic reactions (such as pruritus, rash and urticaria)*. In some cases discontinuation of the treatment may be necessary.
Frequency not known:	Hypersensitivity cutaneous vasculitis*

Metabolism and nutrition disorders

Frequency not known:	Hyperkalaemia* has been reported with heparins and low molecular weight heparins.
	Use of low molecular weight heparins over extended periods has been reported to be associated with development of osteopenia*.
Very rare:	Hyperlipidemia*

Psychiatric disorders

Common:	Confusion

Nervous system disorders

Frequency not known:	Headaches*

Gastrointestinal

Common:	Nausea, diarrhea

Hepatobiliary disorders

Very common:	Asymptomatic and reversible increases in the levels of liver enzymes (e.g. transaminases) have been reported [NOTE: Liver enzymes were not assessed in the Unstable Angina Population].
Frequency not known:	Hepatocellular liver injury*, cholestatic liver injury*

Skin and subcutaneous tissue disorders

Common:	Urticaria, pruritus, erythema
Uncommon:	Bullous dermatitis

Musculoskeletal and connective tissue disorders

Frequency not known:	Osteoporosis following long-term therapy (greater than 3 months)*

General disorders and administration site conditions

Common:	Injection site haematoma, injection site pain, other injection site reaction (such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain or reaction)
Uncommon:	Local irritation
	Skin necrosis*, usually occurring at the injection site, have been reported

with both unfractionated and low molecular weight heparins. These phenomena are usually preceded by purpura or erythematous plaques, infiltrated and painful. Treatment must be discontinued immediately.

Very rare: Pain, haematoma and mild local irritation may follow the subcutaneous injection of enoxaparin*.

Frequency not known: Alopecia*

Hard inflammatory nodules*, which are not cystic enclosures of enoxaparin. They resolve after a few days and should not cause treatment discontinuation.

Investigations

Rare: Hyperkalaemia

Other

Common: Peripheral oedema, fever

c. Description of selected adverse reactions

Haemorrhages

In clinical trials haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most 4.2% in surgical patients receiving prophylaxis. Bleeding may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the use of medications affecting haemostasis (see sections 4.4 and 4.5). Major haemorrhage including retroperitoneal and intracranial bleeding has been reported. Some of these cases have been fatal.

MedDRA system organ class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
Blood and lymphatic symptom disorders	Very common: Haemorrhage* Rare: Retroperitoneal haemorrhage	Common: Haemorrhage*	Very common: Haemorrhage* Uncommon: Intracranial haemorrhage, Retroperitoneal haemorrhage	Common: Haemorrhage* Rare: Retroperitoneal haemorrhage	Common: Haemorrhage* Uncommon: Intracranial haemorrhage, Retroperitoneal haemorrhage

*such as haematoma, ecchymosis other than at injection site, wound haematoma, haematuria, epistaxis and gastro-intestinal haemorrhage.

Thrombocytopenia and thrombocytosis

Mild, transient thrombocytopenia has been reported during the first days of therapy.

MedDRA system organ class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
Blood and lymphatic system disorders	Very common: Thrombocytosis* Common: Thrombocytopenia	Uncommon: Thrombocytopenia	Very common: Thrombocytosis* Common: Thrombocytopenia	Uncommon: Thrombocytopenia	Common: Thrombocytosis* Thrombocytopenia Very rare: Immuno-allergic thrombocytopenia

*Platelet increased >400 10^9/L

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 professionals are asked to report any suspected adverse reactions: https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

Accidental overdosage with Crusia-AFT after intravenous, extracorporeal or subcutaneous administration may lead to haemorrhagic complications through anti-coagulant activity.

Oral ingestion of Crusia-AFT (no reported cases) should lead to no serious consequences, taking into account the very low gastric and intestinal absorption of the product. This may be checked by carrying out a plasma assay of the anti-Xa and anti-IIa activities.

Treatment

The anticoagulant effects can be largely 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 enoxaparin is never completely neutralised (maximum reversal of 60%), even though the anti-coagulant activity is neutralised. (See the prescribing information for protamine salts).

The dose of protamine depends on the dose of Crusia-AFT injected. If Crusia-AFT was administered in the previous 8 hours 1 mg protamine neutralises the anticoagulant effect of 1 mg or 100 anti-heparin units of protamine neutralises the anti-IIa activity generated by 1 mg (100 IU anti-Xa activity) of Crusia-AFT (see the prescribing information for protamine salts). An infusion of 0.5 mg protamine per 1 mg of Crusia-AFT may be administered if Crusia-AFT was administered greater than 8 hours previously, or if it has been determined that a second dose of protamine is required. Protamine administration may not be required 12 hours after the Crusia-AFT injection. However, depending on

the clinical circumstances, e.g. the size of the dose of Crusia-AFT, whether or not a therapeutic level of anticoagulation needs to be retained and whether or not the patient is actively bleeding, the administration of a reduced dose of protamine may not be advisable.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent, heparin group, ATC code: B01A B05

Pharmacodynamic effects

Enoxaparin sodium is a low molecular weight heparin (LMWH) with a mean molecular weight of approximately 4,500 daltons. The drug substance is the sodium salt.
The molecular weight distribution is:
<2000 daltons 12 to 20%
2000 to 8000 daltons 68 to 82%
>8000 daltons ≤18%

Enoxaparin sodium is obtained by alkaline depolymerisation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterised by a 4-enopyranose uronate group at the non-reducing end. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains a 1,6 anhydro derivative on the reducing end of the polysaccharide chain.

In the *in vitro* purified system, enoxaparin sodium has a high anti-Xa activity (approximately 100 IU/mg) and a low anti-IIa or anti-thrombin activity (approximately 28 IU/mg). Pharmacodynamic parameters studied in healthy volunteers at enoxaparin sodium concentration over the range 100–200 mg/ mL were comparable.

Clinical efficacy and safety

Hip replacement surgery

Two randomised single-centre clinical trials were conducted in patients undergoing hip replacement surgery to determine if extended prophylaxis with enoxaparin (Clexane) 40 mg SC daily, given for up to 3 weeks post hospital discharge was effective in reducing the incidence of deep vein thrombosis (DVT) as compared to placebo. All patients were initially treated with Clexane 40 mg SC daily, beginning up to 12 hours prior to surgery in an open-label fashion. Patients who did not exhibit venous thromboembolic disease (either by negative venography in one study or by absence of clinical signs or symptoms in the other study) at the completion of in-hospital treatment were randomised to receive extended prophylaxis with either Clexane (n = 221) or placebo (n = 220) post-discharge in a blinded fashion. The incidence of deep vein thrombosis (total and proximal) during extended prophylaxis was significantly lower for Clexane (total: 12%; proximal: 6%) compared to placebo (total: 28%; proximal:

16%) in both studies. Bleeding events were limited to minor haemorrhages which were 11% for the Clexane treatment group versus 3% for the placebo treatment group. The majority of the bleeding events for both groups were injection site haemorrhages (9% Clexane vs 2% placebo).

Thromboembolism prophylaxis in medical patients

One randomised, double-blind, placebo-controlled, parallel group study was conducted to compare enoxaparin 20 mg once daily (E20), enoxaparin 40 mg once daily and placebo in the prophylaxis of VTE in patients hospitalised with acute heart failure, acute respiratory disease, acute infectious disease, acute rheumatic disorders, or acute inflammatory bowel disease. The treatment lasted 6-14 days. The primary efficacy endpoint was assessed in 866 patients – 288 placebo, 287 E20 and 291 E40 (respectively, 77.6%, 78.8% and 79.3% of those randomised to each group). The incidence of VTE was significantly lower in the E40 group (16/291, 5.5%) than in the placebo group (43/288, 14.9%), with a relative risk of 0.37 (95% CI 0.22-0.63, p = 0.0002). The incidence of VTE in the E20 group (43/287, 15%) was not significantly different from that in the placebo group, with a relative risk of 1.03 (95% CI 0.70-1.51, p = 0.90).

Unstable angina and non-Q-wave myocardial infarction

In an international multicentre study [ESSENCE], 3171 patients enrolled at the acute phase of unstable angina or non-Q-wave myocardial infarction were randomised to receive in association with aspirin (100 to 325 mg once daily), either subcutaneous enoxaparin (Clexane) 1 mg/kg every 12 hours (n = 1607) or intravenous unfractionated heparin adjusted based on activated partial thromboplastin time (aPPT; n = 1564). Patients had to be treated in hospital for a minimum of 2 days and a maximum of 8 days, until clinical stabilisation, revascularisation procedures or hospital discharge; the median duration of treatment was 2.6 days in both groups and patients were followed up to 30 days. Clexane significantly decreased the incidence of recurrent angina, myocardial infarction and death, with an absolute event rate of the composite triple endpoint at day 14 of 16.6% in the Clexane group, compared to 19.8% in the heparin group (p = 0.02). This represented a relative risk reduction of 16.2%, which remained statistically significant at 30 days of follow up. Furthermore, the need for revascularisation with percutaneous, transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) was significantly less frequent in the Clexane group (27.0% vs 32.2%, p = 0.001). The 30 day incidence of major bleeding was not significantly different between the two treatment groups (6.5% in the Clexane group vs 7.0% in the heparin group, p = 0.566), with an increase in minor bleeding observed in the Clexane group (18.4% vs 14.2%, p = 0.001), primarily constituting ecchymoses at injection sites.

Acute ST-segment Elevation Myocardial Infarction (STEMI)

In a multicentre, double-blind, double-dummy, parallel group study, 20,479 patients with STEMI who were eligible to receive fibrinolytic therapy were randomised to receive either enoxaparin (Clexane) or unfractionated heparin. All patients were also treated with aspirin for a minimum of 30 days. Study medication was administered between 15 minutes before and 30 minutes after the initiation of fibrinolytic therapy. Unfractionated heparin was administered beginning with an IV bolus of 60 IU/kg (maximum 4000 IU) and followed by an infusion of 12 IU/kg per hour (initial maximum 1000 IU per hour) that was adjusted to maintain an aPTT of 1.5 to 2.0 times the control value. The IV infusion was

to be given for at least 48 hours. The enoxaparin dosing strategy was adjusted according to the patient's age and renal function. For patients younger than 75 years of age, enoxaparin was given as a single 30 mg intravenous bolus plus a 1 mg/kg SC dose followed by an SC injection of 1 mg/kg every 12 hours. For patients 75 years of age or older, the IV bolus was not given and the SC dose was reduced to 0.75 mg/kg every 12 hours. For patients with severe renal insufficiency (estimated creatinine clearance of less than 30 mL per minute), the dose was to be modified to 1 mg/kg every 24 hours. The SC injections of enoxaparin were given until hospital discharge or for a maximum of eight days (whichever came first).

When percutaneous coronary intervention (PCI) was performed during the study medication period, patients were to receive antithrombotic support with blinded study drug. Therefore, for patients on enoxaparin, the PCI was to be performed on enoxaparin (no switch) using the regimen established in previous studies, i.e. no additional dosing if the last SC administration was given less than 8 hours before balloon inflation; IV bolus of 0.3 mg/kg enoxaparin if the last SC administration was given more than 8 hours before balloon inflation.

A total of 20,506 patients were enrolled in the study, and 20,479 patients were included in the intention to treat (ITT) population. The primary efficacy endpoint was the composite of death from any cause or myocardial reinfarction in the first 30 days after randomisation. The efficacy data show that the rate of the primary efficacy endpoint (death or myocardial re-infarction) was 9.9% in the enoxaparin group, as compared with 12.0% in the unfractionated heparin group, which is a 17% reduction in the relative risk ($P < 0.001$).

The treatment benefits of enoxaparin, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35% reduction in the relative risk of myocardial re-infarction, as compared with unfractionated heparin ($P < 0.0001$). The beneficial effect of enoxaparin on the primary endpoint was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, fibrinolytic administered and time to treatment with study drug.

There was a significant treatment benefit of enoxaparin, as compared with unfractionated heparin, in patients who underwent PCI within 30 days after randomisation (23% relative risk reduction) or who were treated medically (15 % relative risk reduction, $P = 0.27$ for interaction).

The rate of the 30-day composite endpoint of death, myocardial re-infarction or intracranial haemorrhage (a measure of net clinical benefit) was significantly lower ($p < 0.0001$) in the enoxaparin group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favour of treatment with Clexane.

<u>Comparability of Crusia-AFT and Clexane</u>

Equivalent pharmacodynamic (PD) profiles of Crusia-AFT and Clexane have been demonstrated in a single-dose, randomised, double-blind, crossover trial of 46 healthy adults, after administration of 100 mg as a single SC injection. PD bioequivalence was shown in the primary PD parameters A_{max}, $AUEC_{0\text{-}T}$ and $AUEC_{0\text{-}inf}$ for anti-FXa activity and A_{max} and $AUEC_{0\text{-}T}$ for anti-FIIa activity (Table 1).

This bioequivalence was further demonstrated in the secondary PD parameters A_{max}, $AUEC_{0-T}$ and $AUEC_{0-inf}$ for baseline-adjusted TFPI levels (Table 1) and the secondary PD parameter $AUEC_{0-T}$ ratio of anti-FXa activity to anti-FIIa activity (R_{AUEC}).

Table 1:

	Ratio (%) of Geometric LS Means Crusia-AFT/Clexane [95% CI]		
Parameter	Anti-Xa activity	Anti-IIa activity	Baseline-adjusted TFPI levels
A_{max}	100.1 [94.6 – 105.9]	103.3 [94.7 -112.6]	104.1 [95.6 – 113.4]
$AUEC_{0-t}$	103.8 [99.8 – 108.0]	103.5 [90.9 – 117.9]	105.9 [99.1 – 113.1]
$AUEC_{0-inf}$	104.2 [100.0 – 108.6]	-	108.4 [102.1 – 115.2]

Additional supportive evidence of PD bioequivalence was provided by another randomised, double-blind, single-dose, 2-period, 2-sequence cross-over study in 42 healthy adults to determine the PD bioequivalence and the safety and tolerability of Crusia-AFT and US-marketed enoxaparin sodium (Lovenox), after administration of a single SC injection of 100 mg. The results also demonstrated that the test product and the reference product were bioequivalent, based on the PD parameters for anti-Xa activity of $AUEC_{0-T}$, $AUEC_{0-inf}$, and anti-Xa_{max}, as well as for anti-IIa activity of $AUEC_{0-T}$ and anti-IIa_{max}. The PD bioequivalence analyses of the baseline-adjusted TFPI levels and the R_{AUEC} further supported the PD bioequivalence analyses of anti-Xa and anti-IIa activities.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of enoxaparin sodium have been studied primarily in terms of the time course of anti-Xa activity and also by anti-IIa activity, at the recommended dosage ranges after single and repeated subcutaneous administration and after single intravenous administration. The quantitative determination of anti-Xa and anti-IIa pharmacokinetic activities was conducted by validated amidolytic methods with specific substrates and an enoxaparin standard calibrated against the international standard for LMWHs (NIBSC).

Absorption

After subcutaneous (SC) injection of 20 to 80 mg and 1 or 2 mg/kg, enoxaparin sodium is rapidly and completely absorbed. The absorption is directly proportional to the dose administered indicating that, unlike unfractionated heparin, absorption of enoxaparin sodium is linear. The absolute bioavailability of enoxaparin sodium after subcutaneous injection, based on anti-Xa activity, is close to 100%. Injection volume and dose concentration over the range 100-200 mg/mL does not affect pharmacokinetic parameters in healthy volunteers.

The mean maximum plasma anti-Xa activity is observed 3 to 5 hours after subcutaneous injection and achieved approximately 0.2, 0.4, 1.0 and 1.3 anti-Xa IU/mL following single-subcutaneous administration of 20 mg, 40 mg, 1 mg/kg and 1.5 mg/kg doses, respectively.

A 30 mg IV bolus immediately followed by a 1 mg/kg SC every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n = 16) and average exposure corresponding to 88% of steady-state levels. Steady-state is achieved on the second day of treatment.

Enoxaparin pharmacokinetics appears to be linear over the recommended dosage ranges. Intra-patient and inter-patient variability is low. After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg once daily regimens in healthy volunteers, the steady-state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single dose pharmacokinetics. After repeated subcutaneous administration of the 1 mg/kg twice daily regimen, the steady-state is reached from day 3 to 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/mL, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range.

Plasma anti-IIa activity after subcutaneous administration is approximately ten-fold lower than anti-Xa activity. The mean maximum plasma anti-IIa activity is observed approximately 3 to 4 hours following subcutaneous injection and reaches 0.13 IU/mL and 0.19 IU/mL following repeated administration of 1 mg/kg twice daily and 1.5 mg/kg once daily, respectively.

Distribution

The volume of distribution of enoxaparin sodium anti-Xa activity is about 5 litres and is close to the blood volume.

Biotransformation

Enoxaparin sodium is primarily metabolised in the liver by desulfation and/or depolymerisation to lower molecular weight species with much reduced biological potency.

Elimination

Enoxaparin sodium is a low clearance drug with a mean anti-Xa plasma clearance of 0.74 L/h after a 1.5 mg/kg 6-hour intravenous infusion.

Elimination appears monophasic with a half-life of about 4 hours after a single-subcutaneous dose to about 7 hours after repeated dosing. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

Special populations

Renal impairment

A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-50 mL/min) renal impairment after repeated subcutaneous 40 mg once daily doses. In patients with severe renal impairment (creatinine clearance <30 mL/min), the AUC at steady state is significantly increased on

average by 65% after repeated subcutaneous 40 mg once daily doses (see also sections 4.2 and 4.4).

Weight
After repeated subcutaneous 1.5 mg/kg once daily dosing, mean AUC of anti-Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while C_{max} is not increased. There is a lower weight-adjusted clearance in obese subjects with subcutaneous dosing.

When non-weight adjusted dosing was administered, it was found after a single-subcutaneous 40 mg dose, that anti-Xa exposure is 50% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects (see also section 4.4).

Elderly
Based on the results of a population pharmacokinetic analysis, the enoxaparin sodium kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium (see also sections 4.2 and 4.4).

Haemodialysis
In a single study, elimination rate appeared similar but AUC was two-fold higher than control population, after a single 0.25 or 0.50 mg/kg intravenous dose (see also section 4.2).

5.3 Preclinical safety data

In embryo-foetal development studies of enoxaparin there was no evidence of teratogenicity at 30 mg/kg/day SC or 160 mg/kg/day IV in either rats or rabbits. A reduction in rat pup weights occurred at 20 mg/kg/day enoxaparin SC only when administered during the late phase of gestation. An increase in post-implantation loss was noted at 160 mg/kg/day enoxaparin IV in rabbits, but not at 40 mg/kg/day IV, nor in rats at up to 160 mg/kg/day IV. Post-natal development in rats was not affected by doses tested up to a maximum of 20 mg/kg/day enoxaparin IV.

Enoxaparin was not genotoxic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and the *in vivo* rat bone marrow chromosomal aberration test.

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

SC injection
Do not mix with other products.

IV (Bolus) Injection (for acute STEMI indication only)
Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water (see section 4.2).

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Solution for injection in Type I glass prefilled syringes fitted with injection needle, with or without an automatic safety device. Prefilled syringes are packed in plastic blister trays in carton boxes.

Crusia-AFT
20 mg/0.2 mL (anti-Xa: 2,000 IU) prefilled syringes, in packs of 10 and 50 syringes.
40 mg/0.4 mL (anti-Xa: 4,000 IU) prefilled syringes, in packs of 10, 30 and 50 syringes.
60 mg/0.6 mL (anti-Xa: 6,000 IU) prefilled syringes with graduated markings, in packs of 10 and 30 syringes.
80 mg/0.8 mL (anti-Xa: 8,000 IU) prefilled syringes with graduated markings, in packs of 10 and 30 syringes.
100 mg/1 mL (anti-Xa: 10,000 IU) prefilled syringes with graduated markings, in packs of 10 and 30 syringes.

Crusia-AFT (with automatic safety lock system)
20 mg/0.2 mL (anti-Xa: 2,000 IU) prefilled syringes, in packs of 10 and 50 syringes.
40 mg/0.4 mL (anti-Xa: 4,000 IU) prefilled syringes, in packs of 10, 30 and 50 syringes.
60 mg/0.6 mL (anti-Xa: 6,000 IU) prefilled syringes with graduated markings, in packs of 10 and 30 syringes.
80 mg/0.8 mL (anti-Xa: 8,000 IU) prefilled syringes with graduated markings, in packs of 10 and 30 syringes.
100 mg/1 mL (anti-Xa: 10,000 IU) prefilled syringes with graduated markings, in packs of 10 and 30 syringes.

Crusia-AFT Forte
120 mg/0.8 mL (anti-Xa: 12,000 IU) prefilled syringes with double graduated markings, in packs of 10 and 30 syringes.
150 mg/1 mL (anti-Xa: 15,000 IU) prefilled syringes with double graduated markings, in packs of 10 and 30 syringes.

Crusia-AFT Forte (with automatic safety lock system)
120 mg/0.8 mL (anti-Xa: 12,000 IU) prefilled syringes with double graduated markings, in packs of 10 and 30 syringes.
150 mg/1 mL (anti-Xa: 15,000 IU) prefilled syringes with double graduated markings, in packs of 10 and 30 syringes.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AFT Pharmaceuticals Ltd
Level 1, 129 Hurstmere Road
Takapuna
Auckland 0622
Phone: 0800 423 823
Email: customer.service@aftpharm.com

9. DATE OF FIRST APPROVAL

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Summary table of changes:

Section changed	Summary of new information
All	New data sheet.