SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

CRUSIA 20, 2 000 IU (20 mg/0,2 ml) solution for injection in pre-filled syringes

CRUSIA 40, 4 000 IU (40 mg/0,4 ml) solution for injection in pre-filled syringes

CRUSIA 60, 6 000 IU (60 mg/0,6 ml) solution for injection in pre-filled syringes

CRUSIA 80, 8 000 IU (80 mg/0,8 ml) solution for injection in pre-filled syringes

CRUSIA 100, 10 000 IU (100 mg/1 ml) solution for injection in pre-filled syringes

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CRUSIA 20: Each pre-filled syringe contains enoxaparin sodium 2 000 IU anti-Xa activity (equivalent to 20 mg) in 0,2 ml water for injections.

CRUSIA 40: Each pre-filled syringe contains enoxaparin sodium 4 000 IU anti-Xa activity (equivalent to 40 mg) in 0,4 ml water for injections.

CRUSIA 60: Each pre-filled syringe contains enoxaparin sodium 6 000 IU anti-Xa activity (equivalent to 60 mg) in 0,6 ml water for injections.

CRUSIA 80: Each pre-filled syringe contains enoxaparin sodium 8 000 IU anti-Xa activity (equivalent to 80 mg) in 0,8 ml water for injections.

CRUSIA 100: Each pre-filled syringe contains enoxaparin sodium 10 000 IU anti-Xa activity (equivalent to 100 mg) in 1,0 ml water for injections.

For the full list of excipients, see section 6.1.

CRUSIA is sugar free.

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

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringes.

CRUSIA is a clear, sterile solution, free from visible particulate matter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

• To reduce the risk of post-operative venous thrombosis and embolism in high-risk patients (e.g., orthopaedic surgery) and moderate-risk patients (e.g., abdominal surgery).

• To reduce the risk of venous thromboembolism in patients bedridden due to debilitating medical illnesses.

• Treatment of deep venous thrombosis with or without pulmonary embolism. Safety of home treatment for this indication has not been established.

•To reduce the risk of ischaemic complications of unstable angina or non-Q-wave myocardial infarction, within 24 hours of onset, combined with aspirin (100-325 mg daily) for 8 days, or until stabilisation, revascularisation or discharge from hospital.

• To reduce the risk of thrombus formation in extracorporeal 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. Posology and method of administration

To reduce the risk of post-operative venous thrombosis and embolism:

High Risk Patients:

In orthopaedic surgery, 40 mg (0,4 ml) once daily by subcutaneous injection. The first injection should be given, 12 hours pre-operatively.

Treatment is continued for as long as the risk of thromboembolism persists; in general, from 7 to 10 days after surgery or as long as there is a risk of venous thromboembolism until the patient is ambulatory.

Continued therapy with 40 mg once daily for 3 weeks following the initial therapy has been proven to be beneficial in total hip replacement.

Moderate Risk Patients:

In general surgery, 20 mg (0,2 ml) once daily by subcutaneous injection. The first injection should be given 2 hours pre-operatively.

Treatment is continued for as long as the risk of thromboembolism persists; in general, from 7 to 10 days after surgery or as long as there is a risk of venous thromboembolism and until

the patient is ambulatory. For special recommendations concerning dosing intervals for spinal/epidural anaesthesia and percutaneous coronary revascularisation procedures (see section 4.4.).

To reduce the risk of venous thromboembolism in medical patients:

The recommended dose of **CRUSIA** is 40 mg once daily by subcutaneous injection. **CRUSIA** treatment is prescribed for a minimum of 6 days and continued until the return to full ambulation, for a maximum of 14 days.

Treatment of deep vein thrombosis with or without pulmonary embolism:

A dose of 1 mg/kg should be given subcutaneously every 12 hours.

Oral anticoagulant therapy should be initiated when appropriate and **CRUSIA** treatment should be continued until a therapeutic anticoagulant effect has been achieved (International Normalised Ratio 2 to 3). **CRUSIA** treatment is usually prescribed for between 5 and 10 days.

To reduce the risk of ischaemic complications of unstable angina or non-Q-wave myocardial infarction:

The recommended dose of **CRUSIA** is 1 mg/kg every 12 hours by subcutaneous injection, administered concurrently with aspirin (100 to 325 mg once daily). Treatment with **CRUSIA** 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.

To reduce the risk of extracorporeal thrombus during haemodialysis:

The recommended dose is 1 mg/kg of **CRUSIA**. For patients with a high risk of haemorrhage, the dose should be reduced to 0,5 mg/kg for double vascular access or 0,75 mg/kg for single vascular access.

During haemodialysis, **CRUSIA** should be introduced into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4 hour session; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 0,5 to 1 mg/kg may be, given.

Treatment of acute ST-segment Elevation Myocardial Infarction:

The recommended dose of enoxaparin is a single IV bolus of 30 mg plus a 1 mg/kg subcutaneous dose, followed by 1 mg/kg, administered subcutaneously every 12 hours (maximum 100 mg for the first two doses only, followed by 1 mg/kg dosing for the remaining doses). For dosage in patients > 75 years of age; refer to the section on the elderly.

When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific), **CRUSIA** 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 and maintained on an appropriate dose once daily, unless contraindicated.

The recommended duration of **CRUSIA** treatment is 8 days or until hospital discharge, whichever comes first.

For patients managed with Percutaneous Coronary Intervention (PCI):

If the last **CRUSIA** subcutaneous administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last subcutaneous administration was given more than 8 hours before balloon inflation, an IV bolus of 0,3 mg/kg of **CRUSIA** should be administered.

Special populations

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 subcutaneous every 12 hours (maximum 75 mg for the first two doses only, followed by 0,75 mg/kg dosing for the remaining doses).

For other indications, no dose reduction is necessary in the elderly, unless kidney function is impaired (see sections 4.4. (haemorrhage in the elderly); and 4.2. (renal impairment), 5.1 (Elderly).

The efficacy of **CRUSIA** injection in the elderly (> 65 years) was similar to that seen in younger patients (< 65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of **CRUSIA** injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when **CRUSIA** injection was administered at doses of 1,5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of **CRUSIA** injection-associated bleeding increased with age.

Serious adverse events increased with age for patients receiving **CRUSIA** injection. Other clinical experience (including post-marketing surveillance and literature reports) has not revealed additional differences in the safety of **CRUSIA** injection between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially anti-platelet medications) is advised. Monitoring of geriatric patients with low body weight (< 45 kg) and those predisposed to decreased renal function should be considered (see sections 5.1. and 4.4.).

Impaired renal function:

In the absence of safety data on dosages more than 80 mg daily and delayed elimination in patients with severe renal impairment, dosages of more than 60 mg daily should be used

with caution. Special safety vigilance is warranted in patients with severe renal impairment, as there may be an increased bleeding tendency due to the renal failure.

Renal impairment:

See section 4.4. (**Special warnings and precautions for use**) and 5.1 (**Pharmacological properties**).

Severe renal impairment:

A dosage adjustment is required for patients with severe renal impairment (creatinine clearance < 30 ml/min), according to the following tables since **CRUSIA** exposure is significantly increased in this patient population.

The following dosage adjustments are recommended for therapeutic 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
30 mg single IV bolus plus	30 mg single IV bolus plus
a 1 mg/kg SC dose followed by	a 1 mg/kg SC dose followed
1 mg/kg SC twice daily	by 1 mg/kg SC once daily

Elderly patients > 75 years of age (for acute STEM/ indication only)

0,75 mg/kg SC twice daily without initial bolus	1 mg/kg SC once daily without initial bolus

The following dosage adjustments are recommended for 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.

Subcutaneous injection:

CRUSIA is administered by subcutaneous injection for the prevention of venous thromboembolic disease; treatment of deep vein thrombosis; treatment of unstable angina and non-Q-wave myocardial infarction and treatment of acute ST-segment Elevation Myocardial Infarction.

IV bolus injection:

For acute ST-segment Elevation Myocardial Infarction, treatment is to be initiated with a single IV bolus injection immediately followed by a subcutaneous injection.

Arterial line injection:

It is administered through the arterial line of a dialysis circuit for the prevention of thrombus formation in the extra-corporeal circulation during haemodialysis.

Method of administration

CRUSIA must never be injected intramuscularly. The prefilled disposable syringe is ready for immediate use.

Subcutaneous injection technique:

Injections should be made preferably when the patient is lying down. **CRUSIA** is administered by deep subcutaneous injection. Do not expel the air bubble from the syringe before injecting to avoid the loss of medicine, when using the 20 mg and 40 mg prefilled syringes. The administration should be alternated between the left and right anterolateral or posterolateral abdominal wall.

Safety device:

The prefilled syringes fitted with an automatic safety device avoid accidental needle pricks after injecting. When the protective cap is removed off the needle, a drop may appear at the end of the needle. If so, remove it before injecting the medicine by lightly tapping the body of the syringe with the needle pointing down. The prefilled syringe is ready to use. Do not press on the plunger to expel any air bubbles before administering the injection. The injection must be given with the patient preferably lying down. The whole length of the needle should be introduced perpendicularly, not from the side, into a skin fold held between the thumb

and index finger. This skin fold should be held throughout the injection. Do not rub the injection site after administration. The safety device is automatically activated once the plunger is fully depressed, thus completely protecting the used needle and without causing discomfort to the patient. Activation of the safety device is only possible if the plunger is fully depressed.

The safety device can only be activated once the syringe is completely empty.

Intravenous (Bolus) Injection Technique (for acute STEMI indication only):

For intravenous injection, the pre-filled syringe can be used. **CRUSIA** should be administered through an IV line. It should not be mixed or co-administered with other medications. To avoid the possible mixture of **CRUSIA** with other medicines, the IV access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the IV bolus administration of **CRUSIA** to clear the port of medicine. **CRUSIA** may be safely administered with normal saline solution (0,9 %) or 5 % dextrose in water.

4.3. Contraindications

CRUSIA is contraindicated in patients with:

- Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including other low molecular weight heparins (LMWH) or to any of the excipients listed in section 6.1.;
- History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (see also section 4.4.);
- Active clinically significant bleeding and conditions with a high risk of haemorrhage, including recent haemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal, or ophthalmic surgery, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities;
- Spinal or epidural anaesthesia or loco-regional anaesthesia when enoxaparin sodium (e.g., **CRUSIA**) is used for treatment in the previous 24 hours (see section 4.4.).

4.4. Special warnings and precautions for use

Spinal/Epidural anaesthesia:

Spinal/epidural anaesthesia or lumbar puncture must not be performed within 24 hours of administration of CRUSIA at therapeutic doses (see also section 4.3.).

There have been cases of intraspinal haematomas, reported with the concurrent use of CRUSIA and spinal/epidural anaesthesia resulting in long-term or permanent paralysis.

The risk is greater with higher CRUSIA dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional medicines affecting haemostasis such as NSAIDs (refer to interactions with other medicines or other forms of interaction). The risk also appears to be increased by traumatic or repeated neuraxial puncture.

Placement and removal of the catheter is best performed when the anticoagulant effect of CRUSIA is low, however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. For patients with creatinine clearance [15-30 ml/minute], additional considerations are necessary because elimination of enoxaparin sodium is more prolonged (see section 4.2.). Neuraxial techniques should be avoided in patients administered a dose of CRUSIA 2 hours pre-operatively (general surgery).

Placement or removal of a catheter should be delayed for 10-12 hours after administration of DVT prophylactic doses of CRUSIA, whereas patients receiving higher doses of CRUSIA (1 mg/kg twice daily or 1,5 mg/kg once daily) will require longer delays (24 hours). The subsequent CRUSIA dose should be given no sooner than 2 hours after catheter removal.

Should the medical practitioner decide to administer anticoagulation in the context of epidural/spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment 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 medical practitioner 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.

General

CRUSIA cannot be used interchangeably (unit for unit) with other LMWHs. These medicines differ in their manufacturing process, molecular weights, specific anti-Xa and anti-IIa activities, units, dosage and clinical efficacy and safety. This results in differences in pharmacokinetics and associated biological activities (e.g. anti-thrombin activity, and platelet interactions). Special attention and compliance with the instructions for use specific to each proprietary medicine are therefore required.

History of HIT (>100 days)

Heparin-induced thrombocytopenia:

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

CRUSIA is to be used with extreme caution in patients with a history (>100 days) of heparin-induced thrombocytopenia without circulating antibodies. The decision to use **CRUSIA** in such a case must be made only in consultation with an expert in the field and after non-heparin alternative treatments are considered (e.g., danaparoid sodium or lepirudin).

Monitoring of platelet counts

The risk of antibody-mediated HIT also exists with LMWHs. Should thrombocytopenia occur, it usually appears between the 5th and the 21st day following the beginning of **CRUSIA** treatment.

The risk of HIT is higher in postoperative patients and mainly after cardiac surgery and in patients with cancer.

Therefore, it is recommended that the platelet counts be measured before the initiation of therapy with **CRUSIA** and then regularly thereafter during the treatment.

If there are clinical symptoms suggestive of HIT (any new episode of arterial and/or venous thromboembolism, any painful skin lesion at the injection site, any allergic or anaphylactoid reactions on treatment), platelet count should be measured. Patients must be aware that these symptoms may occur and if so, that they should inform their primary care medical practitioner.

In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50 % of the initial value), **CRUSIA** treatment must be immediately discontinued, and the patient switched to another non-heparin anticoagulant alternative treatment.

Haemorrhage

Bleeding may occur at any site because of the anticoagulant effects. If bleeding occurs, the origin of the haemorrhage should be investigated, and appropriate treatment instituted.

CRUSIA should be used with caution in conditions with increased potential for bleeding, such as:

- impaired haemostasis,

- history of peptic ulcer,

- recent ischemic stroke,

- severe arterial hypertension,

- recent diabetic retinopathy,

- neuro- or ophthalmologic surgery,

- concomitant use of medications affecting haemostasis (see section 4.5.).

Laboratory tests

At doses used for prophylaxis of venous thromboembolism, **CRUSIA** 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 activated partial thromboplastin time (aPTT), and activated clotting time (ACT) may occur. Increases in aPTT and ACT are not linearly correlated with increasing enoxaparin sodium antithrombotic activity and therefore, are unsuitable and unreliable for monitoring enoxaparin sodium activity.

Skin necrosis / cutaneous vasculitis

Skin necrosis and cutaneous vasculitis have been reported with LMWHs and should lead to prompt treatment discontinuation.

Percutaneous coronary revascularisation procedures

To minimise the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, NSTEMI and acute STEMI, adhere precisely to the intervals recommended between **CRUSIA** injection 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, sheath should be removed 6 hours after the last IV/SC **CRUSIA** injection. If the treatment with **CRUSIA** 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.

Acute infective endocarditis

Use of heparin is usually not recommended in patients with acute infective endocarditis due to the risk of cerebral haemorrhage. If such use is considered absolutely necessary, the decision must be made only after a careful individual benefit risk assessment.

Mechanical prosthetic heart valves

The use of **CRUSIA** has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received **CRUSIA** 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

The use of **CRUSIA** 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 sodium (100 IU/kg (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 sodium for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism.

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 monitoring is advised, and dose reduction might be considered in patients older than 75 years treated for STEMI (see sections 4.2. and 5.2.).

Renal impairment

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium as contained in **CRUSIA** which increases the risk of bleeding. In these patients, careful clinical monitoring is advised, and biological monitoring by anti-Xa activity measurement might be considered (see sections 4.2. and 5.2.).

CRUSIA is not recommended for patients with end stage renal disease (creatinine clearance <15 ml/min) due to lack of data in this population outside the prevention of thrombus formation in extracorporeal circulation during haemodialysis.

In patients with severe renal impairment (creatinine clearance 15-30 ml/min), since exposure of enoxaparin sodium is significantly increased, a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges (see section 4.2.).

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.

Hepatic impairment

CRUSIA should be used with caution in patients with hepatic impairment due to an increased potential for bleeding. Dose adjustment based on monitoring of anti-Xa levels is unreliable in patients with liver cirrhosis and not recommended (see section 5.2.).

Low weight

An increase in exposure of enoxaparin sodium 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 monitoring is advised in these patients (see section 5.2.).

Obese Patients

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

Hyperkalaemia

Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia (see section 4.8.), particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, taking medicines known to increase potassium (see section 4.5.). Plasma potassium should be monitored regularly especially in patients at risk.

Traceability

LMWHs are biological medicines. In order to improve the LMWH traceability, it is recommended that healthcare providers record the trade name and batch number of the administered product in the patient file.

4.5. Interaction with other medicines and other forms of interaction

Concomitant use not recommended:

- Medicines affecting haemostasis (see section 4.4.)

It is recommended that some medicines which affect haemostasis should be discontinued prior to **CRUSIA** therapy unless strictly indicated. If the combination is indicated, **CRUSIA** should be used with careful clinical and laboratory monitoring when appropriate. These medicines include medicines such as:

- Systemic salicylates, acetylsalicylic acid at anti-inflammatory doses, and NSAIDs including ketorolac,
- Other thrombolytics (e.g., alteplase, reteplase, streptokinase, tenecteplase, urokinase) and anticoagulants (see section 4.2.).

Concomitant use with caution:

The following medicines may be administered with caution concomitantly with **CRUSIA**:

• Other medicines affecting haemostasis such as:

- Platelet aggregation inhibitors including acetylsalicylic acid used at antiaggregant dose (cardio protection), clopidogrel, ticlopidine, and glycoprotein IIb/IIIa antagonists indicated in acute coronary syndrome due to the risk of bleeding,
- Dextran 40,
- Systemic glucocorticoids.

Medicines increasing potassium levels:

Medicines that increase serum potassium levels may be administered concurrently with **CRUSIA** under careful clinical and laboratory monitoring (see sections 4.4. and 4.8.).

4.6. Fertility, pregnancy and lactation

Pregnancy

In humans, there is no evidence that enoxaparin crosses the placental barrier during the second and third trimester of pregnancy. There is no information available concerning the first trimester.

Animal studies have not shown any evidence of fetotoxicity or teratogenicity (see section 5.3.). Animal data have shown that enoxaparin passage through the placenta is minimal.

CRUSIA should be used during pregnancy only if the medical practitioner has established a clear need.

Pregnant women receiving **CRUSIA** should be carefully monitored for evidence of bleeding or excessive anticoagulation and should be warned of the haemorrhagic risk. Overall, the data suggest that there is no evidence for an increased risk of haemorrhage, thrombocytopenia or osteoporosis with respect to the risk observed in non-pregnant women, other than that observed in pregnant women with prosthetic heart valves (see section 4.4.).

If an epidural anaesthesia is planned, it is recommended to withdraw **CRUSIA** treatment before (see section 4.4.).

Breastfeeding

It is not known whether unchanged enoxaparin is excreted in human breast milk. In lactating rats, the passage of enoxaparin or its metabolites in milk is very low. The oral absorption of **CRUSIA** is unlikely. **CRUSIA** syringes can be used during breastfeeding.

Fertility

There are no clinical data for **CRUSIA** in fertility. Animal studies did not show any effect on fertility (see section 5.3.).

4.7. Effects on ability to drive and use machines

CRUSIA has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

a) Summary of the safety profile

It has been reported during clinical trials with enoxaparin sodium, that the enoxaparin sodium regimen administered varied depending on indications. The enoxaparin sodium dose was 4 000 IU (40 mg) SC once daily for prophylaxis of deep vein thrombosis following surgery or in acutely ill medical patients with severely restricted mobility. In treatment of DVT with or without PE, patients receiving enoxaparin sodium were treated with either a 100 IU/kg (1 mg/kg) SC dose every 12 hours or a 150 IU/kg (1,5 mg/kg) SC dose once a day. Reports have shown in the clinical studies for treatment of unstable angina and non-Q-wave myocardial infarction, doses were 100 IU/kg (1 mg/kg) SC every 12 hours, and in the clinical study for treatment of acute STEMI enoxaparin sodium regimen was a 3 000 IU (30 mg) IV bolus followed by 100 IU/kg (1 mg/kg) SC every 12 hours.

It has been reported that 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

Other adverse reactions observed in reported clinical studies and reported in post-marketing experience (* indicates reactions from post-marketing experience) are detailed below.

Blood and lymphatic system disorders	
Frequent:	Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis.
Less frequent:	Eosinophilia*, cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see section 4.4.), neutropenia, leukopenia.
Immune system disorders	
Frequent:	Allergic reaction.
Less frequent:	Anaphylactic/Anaphylactoid reactions including shock*.
Nervous system disorders	
Frequent:	Headache*.
Vascular disorders	
Less frequent:	Spinal haematoma* (or neuraxial haematoma). These reactions

	have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see section 4.4.).
Hepato-biliary disorders	
Frequent:	Hepatic enzyme increases (mainly transaminases > 3 times the upper limit of normality).
Less frequent:	Hepatocellular liver injury *, cholestatic liver injury*, hepatitis.
Skin and subcutaneous tissue disorders	
Frequent:	Urticaria, pruritus, erythema.
Less frequent:	Bullous dermatitis, alopecia*, cutaneous vasculitis*, skin necrosis* usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful). Injection site nodules* (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.
Musculoskeletal, connective tissue and bone disorders	
Less frequent:	Osteoporosis* following long term therapy (greater than 3 months).
General disorders and administration site conditions	
Frequent:	Injection site haematoma, injection site pain, other injection site reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction).
Less frequent:	Local irritation, skin necrosis at injection site.
Investigations	
Less frequent:	Hyperkalaemia* (see sections 4.4. and 4.5.).

c) Description of selected adverse reactions

Haemorrhages

These included major haemorrhages, reported at most in 4,2 % of the patients (surgical patients). Some of these cases have been fatal. In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by haemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products.

Retroperitoneal and intracranial haemorrhages were always considered major.

Haemorrhage may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis (see sections 4.4. and 4.5.).

Blood and lymphatic system disorders				
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**
Frequent Haemorrhage [α]	*Frequent* Haemorrhage [α]	*Frequent* Haemorrhage [α]	*Frequent* Haemorrhage [α]	*Frequent* Haemorrhage [α]
Less frequent Retroperitoneal haemorrhage		*Less frequent* Intracranial haemorrhage, Retroperitoneal haemorrhage	*Less frequent* Retroperitoneal haemorrhage	*Less frequent* Intracranial haemorrhage, Retroperitoneal haemorrhage

[α]: such as haematoma, ecchymosis other than at injection site, wound haematoma, haematuria, epistaxis and gastrointestinal haemorrhage.

Thrombocytopenia and thrombocytosis

Blood and lymphatic system disorders				
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**
Frequent Thrombo-cytosis[β] Thrombo-cytopenia	*Less frequent* Thrombo-cytopenia	*Frequent* Thrombo-cytosis[β] Thrombo-cytopenia	*Less frequent* Thrombo-cytopenia	*Frequent* Thrombo-cytosis[β] Thrombo-cytopenia
				Less frequent Immuno-allergic thrombo-cytopenia

[β]: Platelet increased > 400 G/L

Paediatric population

The safety and efficacy of **CRUSIA** in children have not been established (see section 4.2.).

Reporting of suspected adverse reactions

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

4.9. Overdose

Signs and symptoms

Accidental overdose with enoxaparin sodium after IV, extracorporeal or SC administration may lead to haemorrhagic complications. Following oral administration of even large doses, it is unlikely that **CRUSIA** will be absorbed.

Management

The anticoagulant effects can be largely neutralised by the slow IV injection of protamine. The dose of protamine depends on the dose of **CRUSIA** injected; 1 mg protamine neutralises the anticoagulant effect of 100 IU (1 mg) of enoxaparin sodium, if **CRUSIA** was administered in the previous 8 hours. An infusion of 0,5 mg protamine per 100 IU (1 mg) of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. After 12 hours of the **CRUSIA** injection, protamine administration may not be required. However, even with high doses of protamine, the anti-Xa activity of **CRUSIA** is never completely neutralised (maximum about 60 %) (see the prescribing information for protamine salts).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

CRUSIA is a biosimilar medicine.

Pharmacodynamic effects

Enoxaparin sodium is a low molecular weight heparin with a mean molecular weight of approximately 4 500 daltons, in which the antithrombotic and anticoagulant activities of standard heparin have been dissociated. The medicine substance is the sodium salt.

In the in vitro purified system, enoxaparin sodium has a high anti-Xa activity (approximately 100 IU/mg) and low anti-IIa or anti thrombin activity (approximately 28 IU/mg), with a ratio of 3.6. These anticoagulant activities are mediated through anti-thrombin III (ATIII) resulting in anti-thrombotic activities in humans.

Beyond its anti-Xa/IIa activity, further antithrombotic and anti-inflammatory properties of enoxaparin have been identified in healthy subjects and patients as well as in non-clinical models.

These include ATIII-dependent inhibition of other coagulation factors like factor VIIa, induction of endogenous Tissue Factor Pathway Inhibitor (TFPI) release as well as a reduced release of von Willebrand factor (vWF) from the vascular endothelium into the blood circulation. These factors are known to contribute to the overall antithrombotic effect of enoxaparin sodium.

When used as prophylactic treatment, enoxaparin sodium does not significantly affect the aPTT. When used as curative treatment, aPTT can be prolonged by 1,5-2,2 times the control time at peak activity.

Hepatic impairment

Based on literature data the use of enoxaparin sodium 4 000 IU (40 mg) in cirrhotic patients (Child-Pugh class B-C) appears to be safe and effective in preventing portal vein thrombosis. It should be noted that the literature studies may have limitations. Caution should be used in patients with hepatic impairment as these patients have an increased potential for bleeding (see section 4.4.) and no formal dose finding studies have been performed in cirrhotic patients (Child Pugh class A, B nor C).

5.2. Pharmacokinetic properties

General characteristics

The pharmacokinetic parameters of enoxaparin sodium have been studied primarily in terms of the time course of plasma anti-Xa activity and also by anti-IIa activity, at the recommended dosage ranges after single and repeated SC administration and after single IV administration. The quantitative determination of anti-Xa and anti-IIa pharmacokinetic activities was conducted by validated amidolytic methods.

Absorption

The absolute bioavailability of enoxaparin sodium after SC injection, based on anti-Xa activity, is close to 100 %.

Different doses and formulations and dosing regimens can be used.

The mean maximum plasma anti-Xa activity level is observed 3 to 5 hours after SC injection and achieves approximately 0,2, 0,4, 1,0 and 1,3 anti-Xa IU/ml following single SC administration of 2 000 IU, 4 000 IU, 100 IU/kg and 150 IU/kg (20 mg, 40 mg, 1 mg/kg and 1,5 mg/kg) doses, respectively.

A 3 000 IU (30 mg) IV bolus immediately followed by a 100 IU/kg (1 mg/kg) SC every 12 hours provided initial maximum anti-Xa activity level 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.

After repeated SC administration of 4 000 IU (40 mg) once daily and 150 IU/kg (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. After repeated SC administration of the 100 IU/kg (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 maximum and trough anti-Xa activity levels of about 1,2 and 0,52 IU/ml, respectively.

Injection volume and dose concentration over the range 100-200 mg/ml does not affect pharmacokinetic parameters in healthy volunteers.

Enoxaparin sodium pharmacokinetics appears to be linear over the recommended dosage ranges.

Intra-patient and inter-patient variability is low. Following repeated SC administration, no accumulation takes place.

Plasma anti-IIa activity after SC administration is approximately ten-fold lower than anti-Xa activity. The mean maximum anti-IIa activity level is observed approximately 3 to 4 hours following SC injection and reaches 0,13 IU/ml and 0,19 IU/ml following repeated administration of 100 IU/kg (1 mg/kg) twice daily and 150 IU/kg (1,5 mg/kg) once daily, respectively.

Distribution

The volume of distribution of enoxaparin sodium anti-Xa activity is about 4,3 litres and is close to the blood volume.

Biotransformation

Enoxaparin sodium is primarily metabolised in the liver by desulphation 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 150 IU /kg (1,5 mg/kg) 6-hour IV infusion.

Elimination appears monophasic with a half-life of about 5 hours after a single SC 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

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 sections 4.2. and 4.4.).

Hepatic impairment

In a study conducted in patients with advanced cirrhosis treated with enoxaparin sodium 4 000 IU (40 mg) once daily, a decrease in maximum anti-Xa activity was associated with an increase in the severity of hepatic impairment (assessed by Child-Pugh categories). This decrease was mainly attributed to a decrease in ATIII level secondary to a reduced synthesis of ATIII in patients with hepatic impairment.

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 SC 4 000 IU (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 SC 4 000 IU (40 mg) once daily doses (see sections 4.2. and 4.4.).

Haemodialysis

Enoxaparin sodium pharmacokinetics appeared similar than control population, after a single 25 IU, 50 IU or 100 IU/kg (0,25, 0,50 or 1,0 mg/kg) IV dose however, AUC was two-fold higher than control.

Weight

After repeated SC 150 IU/kg (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 maximum plasma anti-Xa activity level is not increased. There is a lower weight-adjusted clearance in obese subjects with SC dosing.

When non-weight adjusted dosing was administered, it was found after a single SC 4 000 IU (40 mg) dose, that anti-Xa exposure is 52 % higher in low-weight women (<45 kg) and 27

% higher in low-weight men (<57 kg) when compared to normal weight control subjects (see section 4.4.).

Pharmacokinetic interactions

No pharmacokinetic interactions were observed between enoxaparin sodium and thrombolytics when administered concomitantly.

5.3. Preclinical safety data

Besides the anticoagulant effects of enoxaparin sodium, there was no evidence of adverse effects at 15 mg/kg/day in the 13-week SC toxicity studies both in rats and dogs and at 10 mg/kg/day in the 26-week SC and IV toxicity studies both in rats, and monkeys.

Enoxaparin sodium has shown no mutagenic activity based on in vitro tests, including the Ames test, mouse lymphoma cell forward mutation test, and no clastogenic activity based on an in vitro human lymphocyte chromosomal aberration test, and the in vivo rat bone marrow chromosomal aberration test.

Studies conducted in pregnant rats and rabbits at SC doses of enoxaparin sodium up to 30 mg/kg/day did not reveal any evidence of teratogenic effects or fetotoxicity. Enoxaparin sodium was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for injections.

6.2. Incompatibilities

SC injection: Do not mix with other products.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at or below 25 °C.

Do not freeze.

6.5. Nature and contents of container

CRUSIA solution for injection is packed in prefilled syringes.

CRUSIA is packed in clear, transparent Type I glass pre-filled syringes with black chlorobutyl rubber stopper fitted with injection needle with or without an automatic safety device for some presentations.

The needle shield is made of synthetic rubber and a rigid cover of polypropylene.

Prefilled syringes are stored in plastic trays and carton boxes.

CRUSIA 20: 0,2 mL solution for injection in a 0,5 mL pre-filled syringe without scale. Pack sizes of 2, 10 and 50 syringes.

CRUSIA 40: 0,4 mL solution for injection in a 0,5 mL pre-filled syringe without scale. Pack sizes of 2, 10, 30 and 50 syringes.

CRUSIA 60: 0,6 mL solution for injection in a 1,0 mL graduated pre-filled syringe. Pack sizes of 2, 10 and 30 syringes.

CRUSIA 80: 0,8 mL solution for injection in a 1,0 mL graduated pre-filled syringe. Pack sizes of 2, 10 and 30 syringes.

CRUSIA 100: 1,0 mL solution for injection in a 1,0 mL graduated pre-filled syringe. Pack sizes of 2, 10 and 30 syringes.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Pre-filled syringes are ready for immediate use. For method of administration see section 4.2.

Use only clear, colourless solutions.

Pre-filled syringes are supplied with or without an automatic safety system. The instructions for use are presented in the package leaflet.

Each syringe is for single use only. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

1 Sabax Road,

Aeroton,

Johannesburg,

2013

8. REGISTRATION NUMBER(S)

CRUSIA 20: 55/8.2/0009

CRUSIA 40: 55/8.2/0010

CRUSIA 60: 55/8.2/0011

CRUSIA 80: 55/8.2/0012

CRUSIA 100: 55/8.2/0013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2022

10. DATE OF REVISION OF THE TEXT

13 March 2023

PI 13 March 2023