Item Number AIP002146A	Description LBR ENOX CRUSIA 20/40/60/80/ MY	Paper / Grammage Offset 40 g/m² ± 5%	LEAFLET ARTWORK
Replaces ---	Tech. Drawing FO-227 Rev.00 SCALE 1.1	Size 400 x 480 Final Folded Size 120 x 36 Fhinished Folded	
Date 08.03.2021 Proof# 2	Fonts / Typography PDF del cliente	Pharmacode C128: 500214601 Font Size	
Colour/s 1/1 Negro		BUNDLING LABEL Size 12x30	

All dimensions in millimeters

Anverso / *Front*

Tamaño final plegado / *Final folded size*

120 mm

Tamaño final plegado / *Final folded size* 36 mm 36 mm

400 mm

480 mm

CRUSIA® Enoxaparin Sodium Solution for Injection

PRODUCT DESCRIPTION

1. **CRUSIA 2000 IU (20 mg)/0.2 ml Solution for Injection in Pre-filled Syringe** is a clear liquid colourless to pale yellow. Each prefilled syringe contains enoxaparin sodium 2,000 IU anti-Xa activity (equivalent to 20mg) in 0.2 mL water for injections.

2. **CRUSIA 4000 IU (40 mg)/0.4 ml Solution for Injection in Pre-filled** Syringe is a clear liquid colourless to pale yellow. Each prefilled syringe contains enoxaparin sodium 4,000 IU anti-Xa activity (equivalent to 40mg) in 0.4 mL water for injections.

3. **CRUSIA 6000 IU (60 mg)/0.6 ml Solution for Injection in Pre-filled Syringe** is a clear liquid colourless to pale yellow. Each prefilled syringe contains enoxaparin sodium 6,000 IU anti-Xa activity (equivalent to 60mg) in 0.6 mL water for injections.

4. **CRUSIA 8000 IU (80 mg)/0.8 ml Solution for Injection in Pre-filled Syringe** is a clear liquid colourless to pale yellow. Each prefilled syringe contains enoxaparin sodium 8,000 IU anti-Xa activity (equivalent to 80mg) in 0.8 mL water for injections.

CRUSIA is a biosimilar medicine to the reference product CLEXANE.
CRUSIA is not interchangeable or automatically substitutable with CLEXANE.
Note: "enoxaparin sodium" refers to **"CLEXANE"**, while **"biosimilar"** refers to **"CRUSIA".**

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

AIP002146A

CRUSIA (enoxaparin sodium) is indicated in adults for:

• Prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery.

• Prevention of thrombus formation in extracorporeal circulation during haemodialysis.

• Prophylaxis of venous thromboembolic disease in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infection or rheumatic diseases) and reduced mobility at increased risk of venous thromboembolism.

• Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery.

• Acute coronary syndrome:

- Treatment of unstable angina and Non-ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid.

- Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

POSOLOGY AND METHOD OF ADMINISTRATION

POSOLOGY

Prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients

Individual thromboembolic risk for patients can be estimated using validated risk stratification model.

• In patients at moderate risk of thromboembolism, the recommended dose of enoxaparin sodium is 2 000 IU (20 mg) once daily by subcutaneous (SC) injection. Preoperative initiation (2 hours before surgery) of enoxaparin sodium 2 000 IU (20 mg) was proven effective and safe in moderate risk surgery.

In moderate risk patients, enoxaparin sodium treatment should be maintained for a minimal period of 7-10 days whatever the recovery status (e.g., mobility). Prophylaxis should be continued until the patient no longer has significantly reduced mobility.

• In patients at high risk of thromboembolism, the recommended dose of enoxaparin sodium is 4 000 IU (40 mg) once daily given by SC injection preferably started 12 hours before surgery. If there is a need for earlier than 12 hours enoxaparin sodium preoperative prophylactic initiation (e.g., high risk patient waiting for a deferred orthopaedic surgery), the last injection should be administered no later than 12 hours prior to surgery and resumed 12 hours after surgery.

- For patients who undergo major orthopaedic surgery an extended thromboprophylaxis up to 5 weeks is recommended.
- For patients with a high venous thromboembolism (VTE) risk who undergo abdominal or pelvic surgery for cancer an extended thromboprophylaxis up to 4 weeks is recommended.

Prophylaxis of venous thromboembolism in medical patients

The recommended dose of enoxaparin sodium is 4 000 IU (40 mg) once daily by SC injection. Treatment with enoxaparin sodium is prescribed for at least 6 to 14 days whatever the recovery status (e.g., mobility). The benefit is not established for a treatment longer than 14 days.

Treatment of DVT and PE

Enoxaparin sodium can be administered SC either as a once daily injection of 150 IU/kg (1.5 mg/kg) or as twice daily injections of 100 IU/kg (1 mg/kg).

The regimen should be selected by the physician based on an individual assessment including evaluation of the thromboembolic risk and of the risk of bleeding. The dose regimen of 150 IU/kg (1.5 mg/kg) administered once daily should be used in uncomplicated patients with low risk of VTE recurrence. The dose regimen of 100 IU/kg (1 mg/kg) administered twice daily should be used in all other patients such as those with obesity, with symptomatic PE, cancer, recurrent VTE or proximal (vena iliaca) thrombosis. Enoxaparin sodium treatment is prescribed for an average period of 10 days. Oral anticoagulant therapy should be initiated when appropriate (see "Switch between enoxaparin sodium and oral anticoagulants" at the end of section Posology and method of administration).

Prevention of thrombus formation during haemodialysis

The recommended dose is 100 IU/kg (1 mg/kg) of enoxaparin sodium.
For patients with a high risk of haemorrhage, the dose should be reduced to 50 IU/kg (0.5 mg/kg) for double vascular access or 75 IU/kg (0.75 mg/kg) for single vascular access.
During haemodialysis, enoxaparin sodium 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 50 IU to 100 IU/kg (0.5 to 1 mg/kg) may be given.
No data are available in patients using enoxaparin sodium for prophylaxis or treatment and during haemodialysis sessions.

Acute coronary syndrome: treatment of unstable angina and NSTEMI and treatment of acute STEMI.

• For treatment of unstable angina and NSTEMI, the recommended dose of enoxaparin sodium is 100 IU/kg (1 mg/kg) every 12 hours by SC injection administered in combination with antiplatelet therapy. Treatment should be maintained for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days.
Acetylsalicylic acid is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in acetylsalicylic acid-naive patients) and a maintenance dose of 75–325 mg/day long-term regardless of treatment strategy.

• For treatment of acute STEMI, the recommended dose of enoxaparin sodium is a single intravenous (IV) bolus of 3 000 IU (30 mg) plus a 100 IU/kg (1 mg/kg) SC dose followed by 100 IU/kg (1 mg/kg) administered SC every 12 hours (maximum10 000 IU (100 mg) for each of the first two SC doses). Appropriate antiplatelet therapy such as oral acetylsalicylic acid (75 mg to 325 mg once daily) should be administered concomitantly unless contraindicated. The recommended duration of treatment is 8 days or until hospital discharge, whichever comes first. When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific), enoxaparin sodium should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy.

- For dosage in patients ≥ 75 years of age, see paragraph "Elderly".
- For patients managed with PCI, if the last dose of enoxaparin sodium SC was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last SC administration was given more than 8 hours before balloon inflation, an IV bolus of 30 IU/kg (0.3 mg/kg) enoxaparin sodium should be administered

Paediatric population

The safety and efficacy of enoxaparin sodium in paediatric population have not been established.

Elderly

For all indications except STEMI, no dose reduction is necessary in the elderly patients, unless kidney function is impaired (see below "renal impairment" and section Special warnings and special precautions for use).

For treatment of acute STEMI in elderly patients' ≥75 years of age, an initial IV bolus must not be used. Initiate dosing with 75 IU/kg (0.75 mg/kg) SC every 12 hours (maximum 7 500 IU (75 mg) for each of the first two SC doses only, followed by 75 IU/kg (0.75 mg/kg) SC dosing for the remaining doses). For dosage in elderly patients with impaired kidney function, see below "renal impairment" and section Special warnings and special precautions for use.

Hepatic Impairment

Limited data are available in patients with hepatic impairment (see sections Pharmacodynamic properties and Pharmacokinetic properties) and caution should be used in these patients (see section Special warnings and special precautions for use).

Renal Impairment (see sections Special warnings and precautions for use and Pharmacokinetic properties)

• Severe renal impairment
Enoxaparin sodium 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 extra corporeal circulation during haemodialysis.

Dosage table for patients with severe renal impairment (creatinine clearance [15-30] ml/min):

Indication	Dosing regimen
Prophylaxis of venous thromboembolic disease	2 000 IU (20 mg) SC once daily
Treatment of DVT and PE	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of unstable angina and NSTEMI	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of acute STEMI (patients under 75)	1 x 3 000 IU (30 mg) IV bolus plus 100 IU/kg (1 mg/kg) body weight SC and then 100 IU/kg (1 mg/kg) body weight SC every 24 hours
Treatment of acute STEMI (patients over 75)	No IV initial bolus, 100 IU/kg (1mg/kg) body weight SC and then 100 IU/kg (1mg/kg) body weight SC every 24 hours

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.

METHOD OF ADMINISTRATION

CRUSIA syringes should **NOT** be administered by the intramuscular route.
For the prophylaxis of venous thrombo-embolic disease following surgery, treatment of DVT and PE, treatment of unstable angina and NSTEMI, enoxaparin sodium should be administered by SC injection.
• For acute STEMI, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection.
• For the prevention of thrombus formation in the extracorporeal circulation during haemodialysis, it is administered through the arterial line of a dialysis circuit.
The pre-filled disposable syringe is ready for immediate use.

• SC injection technique:
Injection should be made preferably when the patient is lying down. Enoxaparin sodium is administered by deep SC injection.
Do not expel the air bubble from the syringe before the injection to avoid the loss of drug when using pre-filled syringes. When the quantity of drug to be injected requires to be adjusted based on the patient's body weight, use the graduated pre-filled syringes to reach the required volume by discarding the excess before injection. Please be aware that in some cases it is not possible to achieve an exact dose due to the graduations on the syringe, and in such case the volume shall be rounded up to the nearest graduation.
The administration should be alternated between the left and right anterolateral or posterolateral abdominal wall. The whole length of the needle should be introduced vertically into a skin fold gently held between the thumb and index finger. The skin fold should not be released until the injection is complete. Do not rub the injection site after administration.

• IV (bolus) injection (for acute STEMI indication only):
Treatment is to be initiated with a single IV bolus injection, immediately followed by a SC injection.
Enoxaparin sodium should be administered through an IV line. It should not be mixed or co-administered with other medications. To avoid the possible mixture of enoxaparin sodium with other drugs, 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 enoxaparin sodium to clear the port of drug. Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.
- Initial 3 000 IU (30 mg) bolus.
For the initial 3 000 IU (30 mg) bolus, using an enoxaparin sodium graduated pre-filled syringe, expel the excessive volume to retain only 3 000 IU (30 mg) in the syringe. The 3 000 IU (30 mg) dose can then be directly injected into the IV line.
- Additional bolus for PCI when last SC administration was given more than 8 hours before balloon inflation.
An initial IV bolus injection of 3 000 IU followed by an SC injection of 100 IU/kg within 15 minutes, then every 12 hours (a maximum of 10 000 IU for the 1st two SC doses).
The 1st dose of enoxaparin should be administered between 15 minutes before and 30 minutes after the start of thrombolytic therapy (whether fibrin-specific or not).
The recommended duration of treatment is 8 days, or until the patient is discharged from hospital if the hospitalization is less than 8 days.
Concomitant treatment: Aspirin therapy must be instituted as soon as possible after symptoms appear, and continued at a dose of between 75 mg and 325 mg daily for at least 30 days, unless otherwise indicated.
For patients being managed with PCI, an additional IV bolus of 30 IU/kg (0.3 mg/kg) is to be administered if last SC administration was given more than 8 hours before balloon inflation.
In order to assure the accuracy of the small volume to be injected, it is recommended to dilute the drug to 300 IU/ml (3 mg/ml).
To obtain a 300 IU/ml (3 mg/ml) solution, using a 6 000 IU (60 mg) enoxaparin sodium pre-filled syringe, it is recommended to use a 50 ml infusion bag (i.e., using either normal saline solution (0.9%) or 5% dextrose in water) as follows:
Withdraw 30 ml from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 6 000 IU (60 mg) enoxaparin sodium pre-filled syringe into the 20 ml remaining in the bag. Gently mix the contents of the bag. Withdraw the required volume of diluted solution with a syringe for administration into the IV line.
After dilution is completed, the volume to be injected can be calculated using the following formula [Volume of diluted solution (ml) = Patient weight (kg) x 0.1] or using the table below. It is recommended to prepare the dilution immediately before use.
Volume to be injected through IV line after dilution is completed at a concentration of 300 IU (3 mg) /ml.

Weight	Required dose 30 IU/kg (0.3 mg/kg)	Volume to inject when diluted to a final concentration of 300 IU (3 mg) / ml	
[Kg]	IU	[mg]	[ml]
45	1350	13.5	4.5
50	1500	15	5
55	1650	16.5	5.5
60	1800	18	6
65	1950	19.5	6.5
70	2100	21	7
75	2250	22.5	7.5
80	2400	24	8
85	2550	25.5	8.5
90	2700	27	9
95	2850	28.5	9.5
100	3000	30	10
105	3150	31.5	10.5
110	3300	33	11
115	3450	34.5	11.5
120	3600	36	12
125	3750	37.5	12.5
130	3900	39	13
135	4050	40.5	13.5
140	4200	42	14
145	4350	43.5	14.5
150	4500	45	15

• Arterial line injection:
It is administered through the arterial line of a dialysis circuit for the prevention of thrombus formation in the extracorporeal circulation during haemodialysis.
Switch between enoxaparin sodium and oral anticoagulants
• Switch between enoxaparin sodium and vitamin K antagonists (VKA)
Clinical monitoring and laboratory tests [prothrombin time expressed as the International Normalized Ratio (INR)] must be intensified to monitor the effect of VKA. As there is an interval before the VKA reaches its maximum effect, enoxaparin sodium therapy should be continued at a constant dose for as long as necessary in order to maintain the INR within the desired therapeutic range for the indication in two successive tests.
For patients currently receiving a VKA, the VKA should be discontinued and the first dose of enoxaparin sodium should be given when the INR has dropped below the therapeutic range.
• Switch between enoxaparin sodium and direct oral anticoagulants (DOAC)
For patients currently receiving enoxaparin sodium, discontinue enoxaparin sodium and start the DOAC 0 to 2 hours before the time that the next scheduled administration of enoxaparin sodium would be due as per DOAC label.
For patients currently receiving a DOAC, the first dose of enoxaparin sodium should be given at the time the next DOAC dose would be taken.

Administration in spinal/epidural anaesthesia or lumbar puncture.
Should the physician decide to administer anticoagulation in the context of epidural or spinal anaesthesia/analgesia or lumbar puncture, careful neurological monitoring is recommended due to the risk of neuraxial haematomas (see section *Special warnings and special precautions for use*).

• At doses used for prophylaxis
A puncture-free interval of at least 12 hours shall be kept between the last injections of enoxaparin sodium at prophylactic doses and the needle or catheter placement.
For continuous techniques, a similar delay of at least 12 hours should be observed before removing the catheter.
For patients with creatinine clearance [15-30] ml/min, consider doubling the timing of puncture/catheter placement or removal to at least 24 hours.
The 2 hours preoperative initiation of enoxaparin sodium 2 000 IU (20 mg) is not compatible with neuraxial anaesthesia.

• At doses used for treatment
A puncture-free interval of at least 24 hours shall be kept between the last injection of enoxaparin sodium at curative doses and the needle or catheter placement (see also section *Contraindications*).
For continuous techniques, a similar delay of 24 hours should be observed before removing the catheter.
For patients with creatinine clearance [15-30] ml/min, consider doubling the timing of puncture/catheter placement or removal to at least 48 hours
Patients receiving the twice daily doses (i.e. 75 IU/kg (0.75 mg/kg) twice daily or 100 IU/kg (1 mg/kg) twice-daily) should omit the second enoxaparin sodium dose to allow a sufficient delay before catheter placement or removal.
Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial hematoma will be avoided.
Likewise, consider not using enoxaparin sodium until at least 4 hours after the spinal/epidural puncture or after the catheter has been removed. The delay must be 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.

CONTRAINDICATIONS

Enoxaparin sodium **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.
• History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (see Section *Special warnings and special precautions for use*);
• 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 is used for treatment in the previous 24 hours (see section *Special warnings and special precautions for use*).

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

General
Enoxaparin sodium cannot be used interchangeably (unit for unit) with other LMWHs. These medicinal products 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 medicinal product are therefore required.

History of HIT (>100 days)
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 *Contraindications*). Circulating antibodies may persist several years.
Enoxaparin sodium 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 enoxaparin sodium in such a case must be made only after a careful benefit risk assessment 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 enoxaparin sodium 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 enoxaparin sodium 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 physician.
In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50 % of the initial value), enoxaparin sodium treatment must be immediately discontinued and the patient switched to another non-heparin anticoagulant alternative treatment.

Haemorrhage
As with other anticoagulants, bleeding may occur at any site. If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instituted.
Enoxaparin sodium, as with any other anticoagulant therapy, 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 *Interaction with other medicinal products and other forms of interaction).*

Laboratory tests
At doses used for prophylaxis of venous thromboembolism, enoxaparin sodium 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.

Spinal/Epidural anaesthesia or lumbar puncture
Spinal/epidural anaesthesia or lumbar puncture must not be performed within 24 hours of administration of enoxaparin sodium at therapeutic doses (see also section *Contraindications*).
There have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia or spinal puncture procedures resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 4 000 IU (40 mg) once daily or lower. The risk of these events is higher with the use of post-operative indwelling epidural catheters, with the concomitant use of additional drugs affecting haemostasis such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), with traumatic or repeated epidural or spinal 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 sodium and epidural or spinal anaesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium (see section *Pharmacokinetic properties*). Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of enoxaparin sodium 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 *Posology and method of administration*).
Should the physician decide to administer anticoagulation in the context of epidural or spinal anaesthesia/analgesia or lumbar puncture, 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. Instruct patients to report immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

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

Percutaneous coronary revascularization procedures
To minimize 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 enoxaparin sodium 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 enoxaparin sodium injection. If the treatment with enoxaparin sodium 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 hematoma 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 enoxaparin sodium 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 enoxaparin sodium 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 enoxaparin sodium 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 *Posology and method of administration and Pharmacokinetic properties*).

Renal impairment
In patients with renal impairment, there is an increase in exposure of enoxaparin sodium 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 *Posology and method of administration and Pharmacokinetic properties*).
Enoxaparin sodium 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 *Posology and method of administration*).
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
Enoxaparin sodium 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 *Pharmacokinetic properties*).

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 *Pharmacokinetic properties*).

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 Undesirable effects*), particularly inpatients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, taking medicinal products known to increase potassium (see section *Interaction with other medicinal products and other forms of interaction*). Plasma potassium should be monitored regularly especially in patients at risk.

Traceability
LMWHs are biological medicinal products. In order to improve the LMWH traceability, it is recommended that health care professionals record the trade name and batch number of the administered product in the patient file.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Concomitant use not recommended:
• Medicinal products affecting haemostasis (see section *Special warnings and special precautions for use*). It is recommended that some agents which affect haemostasis should be discontinued prior to enoxaparin sodium therapy unless strictly indicated. If the combination is indicated, enoxaparin sodium should be used with careful clinical and laboratory monitoring when appropriate. These agents include medicinal products 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 P*osology and method of administration*).

Concomitant use with caution:
The following medicinal products may be administered with caution concomitantly with enoxaparin sodium:
• Other medicinal products 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.
• Medicinal products increasing potassium levels:
Medicinal products that increase serum potassium levels may be administered concurrently with enoxaparin sodium under careful clinical and laboratory monitoring (see sections *Special warnings and special precautions for use and Undesirable effects*).

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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 foetotoxicity or teratogenic (see section *Preclinical safety data*). Animal data have shown that enoxaparin passage through the placenta is minimal.

Enoxaparin sodium should be used during pregnancy only if the physician has established a clear need.

Pregnant women receiving enoxaparin sodium 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 *Special warnings and special precautions for use*).
If an epidural anaesthesia is planned, it is recommended to withdraw enoxaparin sodium treatment before (see section *Special warnings and special precautions for use*).

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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 enoxaparin sodium is unlikely. CRUSIA can be used during breastfeeding.

Fertility
There are no clinical data for enoxaparin sodium in fertility. Animal studies did not show any effect on fertility (see section *Preclinical safety data*).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Enoxaparin sodium has no or negligible influence on the ability to drive and use machines

UNDESIRABLE EFFECTS

The adverse drug reaction profiles reported in clinical studies that compared CRUSIA to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

Summary of the safety profile
Enoxaparin sodium has been evaluated in more than 15,000 patients who received enoxaparin sodium in clinical trials. These included 1,776 for prophylaxis of deep vein thrombosis following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications, 1,169 for prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility, 559 for treatment of DVT with or without PE, 1,578 for treatment of unstable angina and non-Q-wave myocardial infarction and 10,176 for treatment of acute STEMI.
Enoxaparin sodium regimen administered during these clinical trials varies 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 the treatment of DVT with or without PE, patients receiving enoxaparin sodium were treated with either 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. In the clinical studies for the 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.
In clinical studies, haemorrhages, thrombocytopenia and thrombocytosis were the most commonly reported reactions (see section *Special warnings and special precautions for use* and 'Description of selected adverse reactions' below).

Tabulated summary list of adverse reactions.
Other adverse reactions observed in clinical studies and reported in post-marketing experience (*indicates reactions from post-marketing experience) are detailed below.
Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000 to <1/1 000); and very rare (< 1/10 000) or not known (cannot be estimated from available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders
• Common: Haemorrhage, haemorrhagic anaemia*, thrombocytopenia, thrombocytosis
• Rare: Eosinophilia*, cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see section *Special warnings and special precautions for use*).

Immune system disorders
• Common: Allergic reaction
• Rare: Anaphylactic/Anaphylactoid reactions including shock*

Nervous system disorders
• Common: Headache*

Vascular disorders
• Rare: Spinal haematoma* (or neuraxial haematoma). These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see section *Special warnings and special precautions for use*).

Hepato-biliary disorders
• Very common: Hepatic enzyme increases (mainly transaminases > 3 times the upper limit of normality)
• Uncommon: Hepatocellular liver injury *
• Rare: Cholestatic liver injury*

Skin and subcutaneous tissue disorders
• Common: Urticaria, pruritus, erythema
• Uncommon: Bullous dermatitis
• Rare: 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
• Rare: 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 oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction)
• Uncommon: Local irritation, skin necrosis at the injection site

Investigations
• Rare: Hyperkalaemia* (see sections *Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction*).

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.
As with other anticoagulants, 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 *Special warnings and special precautions for use and Interaction with other medicinal products and other forms of interaction*).

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:* **Haemorrhage**α *Rare:* **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage**α	*Very common:* **Haemorrhage**α *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**	*Common:* **Haemorrhage**α Rare: **Retroperitoneal haemorrhage**	*Common:* **Haemorrhage**α *Uncommon:* **Intracranial haemorrhage, Retroperitoneal haemorrhage**

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

Thrombocytopenia and thrombocytosis

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**β *Rare:* **Thrombocytopenia**	*Uncommon:* **Thrombocytopenia**	*Very common:* **Thrombocytosis**β *Common:* **Thrombocytopenia**	*Uncommon:* **Thrombocytopenia**	*Common:* **Thrombocytosis**β **Thrombocytopenia** *Very rare:* **Immuno-allergic thrombocytopenia**

β: Platelet increased >400 G/L

Paediatric population
The safety and efficacy of enoxaparin sodium in children have not been established (see section *Posology and method of administration*).

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 enoxaparin sodium will be absorbed.
Management
The anticoagulant effects can be largely neutralized by the slow IV injection of protamine. The dose of protamine depends on the dose of enoxaparin sodium injected;
• 1 mg protamine neutralizes the anticoagulant effect of 100 IU (1 mg) of enoxaparin sodium, if enoxaparin sodium 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 enoxaparin sodium injection, protamine administration may not be required.
However, even with high doses of protamine, the anti-Xa activity of enoxaparin sodium is never completely neutralized (maximum about 60%) (see the prescribing information for protamine salts).

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC EFFECTS
Pharmacotherapeutic group: **ANTITHROMBOTIC AGENT**, ATC code: **B01 AB05**:
Enoxaparin is a low-molecular-weight heparin with a mean molecular weight of approximately 4500 daltons, in which the antithrombotic and anticoagulant activities of standard heparin have been dissociated. The drug 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 antithrombin activity (approximately 28IU/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 to 2.2 times the control time at peak activity.

CLINICAL EFFICACY AND SAFETY

COMPARATIVE CLINICAL TRIALS

A Single-Dose, randomized, double-blind, two-way crossover pivotal study was conducted to demonstrate the pharmacodynamic equivalence of CRUSIA to CLEXANE (European reference biologic) (Study# ROV-RO20-2015-01).

Efficacy
Efficacy is based on the data from the two pharmacodynamics (PD) clinical trials demonstrating equivalence in primary and secondary PD endpoints using a 95% confidence interval. The 95% CI of the ratio of the geometric least squares means between CRUSIA and CLEXANE for $AUEC_{0\text{-}inf}$, $AUE_{C0\text{-}T}$, and anti-Xa_{max} of anti-Xa activity, and $AUE_{C0\text{-}T}$ and anti-IIa_{max} of anti-IIa activity met the equivalence interval 80% to 125%, thereby demonstrating pharmacodynamic biosimilarity of CRUSIA to CLEXANE. The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG (CLEXANE)

Prevention of venous thromboembolic disease associated with surgery

Extended prophylaxis of VTE following orthopaedic surgery
In a double-blind study of extended prophylaxis for patients undergoing hip replacement surgery, 179 patients with no venous thromboembolic disease initially treated, while hospitalized, with enoxaparin sodium 4 000 IU (40 mg) SC, were randomized to a post-discharge regimen of either enoxaparin sodium 4 000 IU (40 mg) (n=90) once a day SC or to placebo (n=89) for 3 weeks. The incidence of DVT during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo, no PE was reported. No major bleeding occurred. The efficacy data are provided in the table below.

	Enoxaparin sodium 4 000 IU (40 mg) once a day SC n (%)	Placebo once a day SC n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Total VTE	6 (6.6)	18 (20.2)
• Total DVT (%)	6 (6.6) *	18 (20.2)
• Proximal DVT (%)	5 (5.6) #	7 (8.8)
*p value versus placebo =0.008 #p value versus placebo =0.537		

In a second double-blind study, 262 patients without VTE disease and undergoing hip replacement surgery initially treated, while hospitalized, with enoxaparin sodium 4 000 IU (40 mg) SC were randomized to a post-discharge regimen of either enoxaparin sodium 4 000 IU (40 mg) (n=131) once a day SC or to placebo (n=131) for 3 weeks. Similar to the first study the incidence of VTE during extended prophylaxis was significantly lower for enoxaparin sodium compared to placebo for both total VTE (enoxaparin sodium: 21 [16%] versus placebo: 45 [34.4%]; p=0.001) and proximal DVT (enoxaparin sodium: 8 [6.1%] versus placebo: 28 [21.4%]; p=<0.001). No difference in major bleeding was found between the enoxaparin sodium and the placebo group.

Extended prophylaxis of DVT following cancer surgery
A double-blind, multicenter trial, compared a four-week and a one-week regimen of enoxaparin sodium prophylaxis in terms of safety and efficacy in 332 patients undergoing elective surgery for abdominal or pelvic cancer. Patients received enoxaparin sodium (4 000 IU (40 mg) SC) daily for 6 to 10 days and were then randomly assigned to receive either enoxaparin sodium or placebo for another 21 days. Bilateral venography was performed between days 25 and 31, or sooner if symptoms of venous thromboembolism occurred. The patients were followed for three months. Enoxaparin sodium prophylaxis for four weeks after surgery for abdominal or pelvic cancer significantly reduced the incidence of venographically demonstrated thrombosis, as compared with enoxaparin sodium prophylaxis for one week. The rates of venous thromboembolism at the end of the double-blind phase were 12.0 % (n=20) in the placebo group and 4.8% (n=8) in the enoxaparin sodium group; p=0.02. This difference persisted at three months [13.8% vs. 5.5% (n=23 vs 9), p=0.01]. There were no differences in the rates of bleeding or other complications during the double-blind or follow-up periods.

Prophylaxis of venous thromboembolic disease in medical patients with an acute illness expected to induce limitation of mobility
In a double blind multicentre, parallel group study, enoxaparin sodium 2 000 IU (20 mg) or 4 000 IU (40 mg) once a day SC was compared to placebo in the prophylaxis of DVT in medical patients with severely restricted mobility during acute illness (defined as walking distance of <10 meters for ≤3 days). This study included patients with heart failure (NYHA Class III or IV); acute respiratory failure or complicated chronic respiratory insufficiency, and acute infection or acute rheumatic; if associated with at least one VTE risk factor (age ≥75 years, cancer, previous VTE, obesity, varicose veins, hormone therapy, and chronic heart or respiratory failure).
A total of 1,102 patients were enrolled in the study, and 1,073 patients were treated. Treatment continued for 6 to 14 days (median duration 7 days). When given at a dose of 4 000 IU (40 mg) once a day SC, enoxaparin sodium significantly reduced the incidence of VTE as compared to placebo. The efficacy data are provided in the table below.

	Enoxaparin sodium 2 000 IU (20 mg) once a day SC n (%)	Enoxaparin sodium 4 000 IU (40 mg) once a day SC n (%)	Placebo n (%)
All Treated Medical Patients During Acute Illness	287 (100)	291(100)	288 (100)
Total VTE	43 (15.0)	16 (5.5) *	43 (14.9)
Total DVT (%)	43 (15.0)	16 (5.5)	40 (13.9)
Proximal DVT (%)	13 (4.5)	5 (1.7)	14 (4.9)

VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin
* p value versus placebo =0.0002

At approximately 3 months following enrolment, the incidence of VTE remained significantly lower in the enoxaparin sodium 4 000 IU (40 mg) treatment group versus the placebo treatment group. The occurrence of total and major bleeding were respectively 8.6% and 1.1% in the placebo group, 11.7% and 0.3% in the enoxaparin sodium 2 000 IU (20 mg) group and 12.6% and 1.7% in the enoxaparin sodium 4 000 IU (40 mg) group.

Treatment of deep vein thrombosis with or without pulmonary embolism
In a multicentre, parallel group study, 900 patients with acute lower extremity DVT with or without PE were randomized to an inpatient (hospital) treatment of either (i) enoxaparin sodium 150 IU/kg (1.5 mg/kg) once a day SC, (ii) enoxaparin sodium 100 IU/kg (1 mg/kg) every 12 hours SC, or (iii) heparin IV bolus (5 000 IU) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). A total of 900 patients were randomized in the study and all patients were treated. All patients also received warfarin sodium (dose adjusted according to prothrombin time to achieve an INR of 2.0 to 3.0), commencing within 72 hours of initiation of enoxaparin sodium or standard heparin therapy, and continuing for 90 days. Enoxaparin sodium or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved. Both enoxaparin sodium regimens were equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism (DVT and/or PE). The efficacy data are provided in the table below.

	Enoxaparin sodium 150 IU/kg (1.5 mg/kg) once a day SC n (%)	Enoxaparin sodium 100 IU/kg (1 mg/kg) twice a day SC n (%)	Heparin aPTT Adjusted IV Therapy n (%)
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)
Total VTE	13 (4.4) *	9 (2.9)*	12 (4.1)
• DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)
• Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
• PE (%)	2 (0.7)	2 (0.6)	4 (1.4)

VTE = venous thromboembolic event (DVT and/or PE)
*The 95% Confidence Intervals for the treatment differences for total VTE were:
• enoxaparin sodium once a day versus heparin (-3.0 to 3.5)
• enoxaparin sodium every 12 hours versus heparin (-4.2 to 1.7).

Major bleeding were respectively 1.7% in the enoxaparin sodium 150 IU/kg (1.5 mg/kg) once a day group, 1.3% in the enoxaparin sodium 100 IU/kg (1 mg/kg) twice a day group and 2.1% in the heparin group.

Treatment of unstable angina and non ST elevation myocardial infarction
In a large multicentre study, 3,171 patients enrolled at the acute phase of unstable angina or non-Q- wave myocardial infarction were randomized to receive in association with acetylsalicylic acid (100 to 325 mg once daily), either enoxaparin sodium 100 IU/kg (1 mg/kg) every 12 hours or IV unfractionated heparin adjusted based on aPTT. Patients had to be treated in hospital for a minimum of 2 days and a maximum of 8 days, until clinical stabilization, revascularization procedures or hospital discharge. The patients had to be followed up to 30 days. In comparison with heparin, enoxaparin sodium significantly reduced the combined incidence of angina pectoris, myocardial infarction and death, with a decrease of 19.8 to 16.6% (relative risk reduction of 16.2%) on day 14. This reduction in the combined incidence was maintained after 30 days (from 23.3 to 19.8%; relative risk reduction of 15%). There were no significant differences in major haemorrhages, although a haemorrhage at the site of the SC injection was more frequent.

Treatment of acute ST-segment elevation myocardial infarction
In a large multicentre study, 20 479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either: enoxaparin in a single 3 000 IU (30 mg) IV bolus plus a 100 IU/kg (1 mg/kg) SC dose followed by an SC injection of 100 IU/kg (1 mg/kg) every 12 hours, or IV unfractionated heparin adjusted based on aPTT for 48 hours. All patients were also treated with acetylsalicylic acid for a minimum of 30 days. The enoxaparin sodium dosing strategy was adjusted for severe renally impaired patients and for the elderly of at least 75 years of age. The SC injections of enoxaparin sodium were given until hospital discharge or for a maximum of eight days (whichever came first). 4716 patients underwent percutaneous coronary intervention (PCI) receiving antithrombotic support with blinded study drugs. Therefore, for patients on enoxaparin sodium, the PCI was to be performed on enoxaparin sodium (no switch) using the regimen established in previous studies i.e., no additional dosing, if last SC administration given less than 8 hours before balloon inflation, IV bolus of 30 IU/kg (0.3 mg/kg) enoxaparin sodium, if the last SC administration given more than 8 hours before balloon inflation.
Enoxaparin sodium compared to unfractionated heparin significantly decreased the incidence of the primary end point, a composite of death from any cause or myocardial reinfarction in the first 30 days after randomization [9.9% in the enoxaparin group versus 12.0% in the unfractionated heparin group] with a 17% relative risk reduction (p<0.001).
The treatment benefits of enoxaparin sodium, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35 percent reduction in the relative risk of myocardial re-infarction, as compared with treatment with unfractionated heparin (p<0.001).
The beneficial effect of enoxaparin sodium on the primary endpoint was consistent across key sub-groups including age, gender, infarct location, history of diabetes or prior myocardial infarction, type of thrombolytic administered and time to treatment with study drug.
There was a significant treatment benefit of enoxaparin sodium, as compared with unfractionated heparin, in patients who underwent percutaneous coronary intervention within 30 days after randomization (23% reduction in relative risk) or who were treated medically (15% reduction in relative risk, 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 sodium group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favour of treatment with enoxaparin sodium.
The incidence of major bleeding at 30 days was significantly higher (p<0.0001) in the enoxaparin sodium group (2.1%) versus the heparin group (1.4%). There was a higher incidence of gastrointestinal bleeding in the enoxaparin group (0.5%) versus the heparin group (0.1%), while the incidence of intracranial haemorrhage was similar in both groups (0.8% with enoxaparin sodium versus 0.7% with heparin).
The beneficial effect of enoxaparin sodium on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period.
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 *Special warnings and precautions for Use*) and no formal dose finding studies have been performed in cirrhotic patients (Child Pugh class A, B nor C).

PHARMACOKINETIC PROPERTIES
General characteristics
The pharmacokinetic parameters of enoxaparin sodium have been studied primarily in terms of the time course of plasma anti-Xa and also by anti-IIa activity, at the recommended dosage ranges after single and repeated sub-cutaneous administration, and after single intravenous injection. 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 dosses 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 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.
An 3 000 IU (30 mg) IV bolus immediately followed by 100 IU/kg (1 mg/kg) SC every 12 hours provided initial maximum anti- Xa activity 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
After repeated SC administration of 4 000 anti-Xa 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 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 10-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 anti-IIa IU/ml and 0.91 IU/ml following repeated administration of a 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 liters and is close to the blood volume.

Biotransformation
Enoxaparin sodium is primarily metabolized mainly in the liver by desulfation and/or depolymerization 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 Section *Special warnings and special precautions for use*).

Hepatic impairment
In a study conducted in patients with advanced cirrhosis treated with enoxaparin sodium 4000 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 Posology and method of administration and Special warnings and special precautions for use).

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/m2) 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- weightmen (<57 kg) when compared to normal weight control subjects (see section *Special warnings and special precautions for use*).

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

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 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 20 mg/kg/day.

COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY
Comparative Non-Clinical Pharmacodynamics
In vitro Studies
Five batches of CRUSIA and five batches of CLEXANE were used to determine the in vitro concentration-response effect on the percentage of anti-Factor Xa and anti-Factor IIa activities inhibition. The percentage of inhibition was calculated and adjusted to a 4 parameter logistic regression (i.e.4PL). From the adjusted curves, the IC50 was calculated for each batch and for each activity. The IC50 values obtained were between 2.97 and 3.99 mcg/mL for anti-Factor Xa activity and between 5.75 and 7.71 mcg/mL for anti-Factor IIa activity. The 90% Confidence Interval of the ratio of the geometric means was within the interval for similarity, thereby demonstrating equivalence between CRUSIA and CLEXANE.

STORAGE CONDITION
Do not store above 25°C. Do not freeze. Keep out of the reach of children.

SHELF LIFE
36 months – 3 years

PRESENTATIONS
For **CRUSIA 2 000 IU (20 mg)/0.2 ml; CRUSIA 4000 IU (40 mg)/0.4 ml; CRUSIA 6000 IU (60 mg)/0.6 ml; and CRUSIA 8000 IU (80 mg)/0.8 ml:**
Solution for injection in Type I glass pre-filled syringes with chlorobutyl rubber stopper fitted with injection needle and with or without an automatic safety device. 2 or 10 Prefilled syringes are stored in plastic trays, packed in unit carton boxes and enclosed with a package insert.

Manufactured and released by:
Rovi Pharma Industrial Services, S.A.
Julian Camarillo, 35,
28037 Madrid
Espana / Spain

Product Owner:
Laboratorios Farmaceuticos Rovi, S.A.,
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480 mm