Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clexane Syringes 100mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clexane Syringes (100mg/ml)

20mg Injection	Enoxaparin sodium 20mg (equivalent to 2,000 IU anti-Xa activity) in 0.2ml water for injections
40mg Injection	Enoxaparin sodium 40mg (equivalent to 4,000 IU anti-Xa activity) in 0.4ml water for injections

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.
Product imported from Spain:
Sterile pryogen-free solution for injection contained in ready-to-use pre-filled syringes.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The prophylaxis of thromboembolic disorders of venous origin, in particular those which may be associated with orthopaedic or general surgery.
The prophylaxis of venous thromboembolism in medical patients bedridden due to acute illnesses including cardiac insufficiency, respiratory failure, or severe infections.
The treatment of venous thromboembolic disease presenting with deep vein thrombosis, pulmonary embolism or both.
The treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).
The prevention of thrombus formation in the extracorporeal circulation during haemodialysis.

4.2 Posology and method of administration

Adults:
Prophylaxis of venous thromboembolism in surgical patients
In patients with a moderate risk of venous thromboembolism, the recommended dosage of enoxaparin sodium is 20mg (2,000 IU) once daily by subcutaneous injection. In patients undergoing surgery, the initial dose should be given approximately 2 hours pre-operatively.

In patients with a higher risk of thromboembolism, such as in orthopaedic surgery, the recommended dosage of enoxaparin sodium given by subcutaneous injection is 40mg (4,000 IU) once daily with the initial dose administered approximately 12 hours pre-operatively.

Enoxaparin sodium treatment is usually prescribed for an average period of 7 to 10 days, or until the risk of thromboembolism has diminished.

Longer treatment duration may be appropriate in some patients following hip replacement and enoxaparin sodium may be continued for as long as there is a risk of venous thrombo-embolism and until the patient is ambulatory.

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

For special recommendations concerning dosing intervals for Spinal/Epidural Anaesthesia and Percutaneous coronary revascularisation procedures: see Precautions & Warnings section.

Prophylaxis of venous thromboembolism in medical patients
The recommended dose of enoxaparin sodium is 40mg once daily by subcutaneous injection. Treatment with enoxaparin is prescribed for a minimum of 6 days and continued until the full return to ambulation, for a maximum of 14 days. Where a patient is clinically adjudged to be at continued significant risk for thromboembolic events beyond fourteen days a decision to prolong prophylaxis should be made on an individual basis.

Treatment of venous thromboembolic disease presenting with deep vein thrombosis, pulmonary embolism or both
Enoxoparin sodium can be administered subcutaneously either as a single injection of 1.5mg/kg (150 IU/kg) or as a twice daily injection of 1 mg /kg (100 IU/kg). In patients with a complicated thromboembolic disorder, a dose of 1mg/kg (100 IU/kg) administered twice daily is recommended.
Enoxaparin treatment is usually prescribed for at least 5 days and until adequate oral anticoagulation is established.

Treatment of unstable angina and non-Q-wave myocardial infarction:
The recommended dose 1mg/kg (100 IU/kg) every 12 hours by subcutaneous injection, administered concurrently with oral aspirin (100 to 325mg once daily). Enoxaparin treatment should be prescribed for a minimum of 2 days and continued until clinical stabilisation. The usual duration of treatment is 2 to 8 days.

Prevention of extracorporeal thrombus formation during haemodialysis:
A dose of 1mg/kg (100 IU/kg) introduced into the arterial line at the beginning of a dialysis session is usually sufficient for a 4 hour session. If fibrin rings are found, such as after a longer than normal session, a further dose of 0.5 to 1mg/kg (50 to 100 IU/kg) may be given. For patients at a high risk of haemorrhage the dose should be reduced to 0.5mg/kg (50 IU/kg) for double vascular access or 0.75mg/kg (75 IU/kg) for single vascular access.

Treatment of acute ST-segment Elevation Myocardial Infarction:
The recommended dose of enoxaparin sodium is a single IV bolus of 30mg plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours (max 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, see section on Elderly.

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. All patients should receive acetylsalicylic acid (ASA) as soon as they are identified as having STEMI and maintained under (75 to 325 mg once daily) unless contraindicated.

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

For patients managed with Percutaneous Coronary Intervention (PCI: if the last enoxaparin sodium SC administration was given less that 8 hours before balloon inflation, no additional dosing is needed. If the last SC administration was giving more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of enoxaparin sodium should be administered.

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

For other indications, no dose adjustment is necessary in the elderly, unless kidney function is impaired (see Warnings & Precautions: Haemorrhage in the Elderly, Pharmacokinetics: Elderly and Posology and Method of Administration: Renal impairment).

Children:
Not recommended, as dosage not established.

Renal impairment:
(see Warnings & Precautions: Renal impairment and Pharmacokinetics: Renal impairment).

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

The following dosage adjustments are recommended for therapeutic dosage ranges:

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

The following dosage adjustment are recommended for prophylactic dosage ranges:

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

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

Moderate and Mild Renal Impairment:
Although no adjustment of the dose is recommended in patients with moderate (creatinine clearance 30-50ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised.

Hepatic impairment:
In the absence of clinical studies, caution should be exercised.

Administration

Bodyweight:
No dosage adjustments are recommended in obesity or low body weight (see also section 4.4 Special warnings and precautions for use: *Low body weight and Monitoring*; section 5.2 Pharmacokinetic properties).
Clexane is administered by subcutaneous injection for the prevention of venous thromboembolic disease, treatment of deep vein thrombosis or for the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST elevation

myocardial infarction (STEMI); through the arterial line of a dialysis circuit for the prevention of thrombus formation in the extra-corporeal circulation during haemodialysis; and via intravenous (bolus) injection through an intravenous line only for the initial dose of acute STEMI indication and before PCI when needed. It must not be administered by the intramuscular route.

To avoid accidental needle stick injury after injection, the prefilled syringes are fitted with an automatic safety device The pre-filled disposable syringe is ready for immediate use.

Subcutaneous injection technique:
The pre-filled disposable syringe is ready for immediate use. Clexane should be administered when the patient is lying down, by deep subcutaneous injection. The air bubble should not be expelled from the syringe before the injection is given to avoid the loss of drug. 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 held between the thumb and index finger. The skin fold should not be released until the injection is complete. Once the plunger is fully pressed down the safety device is activated automatically. This protects the used needle. Note: The plunger has to be pressed down all the way for the safety device to be activated.
Do not rub the injection site after administration.

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

Initial 30-mg bolus
For the initial 30-mg bolus, using an enoxaparin sodium graduated pre-filled syringe, expel the excessive volume to retain only 30 mg (0.3 ml) in the syringe. The 30-mg dose can then be directly injected into the intravenous line.

Additional bolus for PCI when last SC administration was given more than 8 hours before balloon inflation:
For patients being managed with Percutaneous Coronary Intervention (PCI), an additional IV bolus of 0.3mg/kg is to be administered if last SC administration was given more than 8 hours before balloon inflation (see Section 4.2: Treatment of acute STEMI).

In order to assure the accuracy of the small volume to be injected, it is recommended to dilute the drug to 3 mg/ml.

To obtain a 3-mg/ml solution, using a 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 60-mg exnoxaparin 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 intravenous 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 intravenous line after dilution is completed

Weight [kg]	Required dose (0.3 mg/kg) [mg]	Volume to inject when diluted to a final concentration of 3 mg/ml [ml]
45	13.5	4.5
50	15	5
55	16.5	5.5
60	18	6
65	19.5	6.5
70	21	7
75	22.5	7.5
80	24	8
85	25.5	8.5
90	27	9
95	28.5	9.5

100	30	10

4.3 Contraindications

Contraindicated in patients with acute bacterial endocarditis; active major bleeding disorders and conditions with a high risk of uncontrolled haemorrhage, including recent hemorrhagic stroke or subdural haematoma; thrombocytopenia in patients with a positive in-vitro aggregation test in the presence of enoxaparin; in jaundice; active gastric or duodenal ulceration; hiatal ulceration; threatened abortion, or retinopathy Hypersensitivity to enoxaparin, heparin or its derivates including other Low Molecular Weight Heparins.

4.4 Special warnings and precautions for use

General
Low Molecular Weight Heparins should not be used interchangeably since they differ in their manufacturing process, molecular weights, specific anti Xa activities, units and dosage. This results in differences in pharmacokinetics and associated biological activities (e.g. anti-IIa activity, and platelet interactions). Special attention and compliance with the instructions for use specific to each proprietary medicinal product are therefore required.

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

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

Placement or removal of a catheter should be delayed for 10-12 hours after administration of DVT prophylactic doses of enoxaparin sodium, whereas patients receiving higher doses of enoxaparin sodium (1mg/kg twice daily or 1.5 mg/kg once daily) will require longer delays (24 hours). The subsequent enoxaparin sodium dose should be given no sooner than two hours after catheter removal.

Should the physician 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 the lower limbs), bowel and/or bladder dysfunction. Patients should be instructed to inform their physician immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal haematoma are suspected urgent diagnosis and treatment including spinal cord decompression should be initiated.

Heparin induced thrombocytopenia
Enoxaparin is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia with or without thrombosis.

Precutaneous coronary revascularisation procedures
To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between Clexane injection doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device used, the sheath can be removed immediately. If manual compression method is used, sheath should be removed 6 hours after last 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.

Pregnant Women with Mechanical Prosthetic Heart Valves:
The use of clexane 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 (1mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and foetal death. There have been isolated post-marketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see Section 4.5: Mechanical prosthetic heart valves).

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 aPTT (activated partial thromboplastin time) and ACT (activated clotting time) 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.

Do not administer by the intramuscular route.

Haemorrhage
As with other anticoagulants, bleeding may occur at any site. If bleeding, the origin of the haemorrhage should be investigated and appropriate treatment instituted.

Use in conditions with increased potential for bleeding
Enoxaparin injection, as with any other anticoagulant therapy, should only be used with great caution in conditions with increased potential for bleeding, such as:

- impaired haemostasis,
- history of peptic ulcer or bleeding,
- recent ischaemic stroke,
- uncontrolled severe arterial hypertension,
- severe liver or kidney dysfunction,
- diabetic retinopathy,
- recent ophthalmologic or neuro surgery or trauma
- concomitant use of medications affecting hemostasis (see Section 4.5).

Mechanical Prosthetic Heart Valves:
The use of clexane 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 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 valves may be at higher risk for thromboembolism (see Section 4.5: Pregnant women with mechanical prosthetic heart valves).

Haemorrhage in the Elderly:
No increased bleeding tendency is observed in the elderly with the prophylactic dosage ranges. Elderly patients (especially patients eighty years of age and older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges. Careful clinical monitoring is advised (see Section 4.2: Elderly and Section 5.2: Elderly).

Renal impairment
In patients with renal impairment, there is an increase in exposure of enoxaparin sodium which increases the risk of bleeding. Since exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30ml/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50ml/min) and mild (creatinine clearance 50-80ml/min) renal impairment, careful monitoring is advised (see Section 4.2: Renal impairment and Section 5.2: Renal impairment).

Low Weight
An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45kg) and low-weight men(<57kg) which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients (see Section 5.2:Weight).

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

Monitoring of platelet counts
As there is a risk of antibody-mediated heparin-induced thrombocytopenia also occurring with low molecular weight heparins, regular platelet count monitoring should be considered prior to and during therapy with these agents. Thrombocytopenia, should it occur, usually appears between the 5th and 21st day following the beginning of therapy and may be complicated by thrombosis. Therefore, it is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin and then regularly thereafter during the treatment. If the platelet count is significantly reduced (30 to 50% of the initial value), or thrombosis occurs, therapy must be discontinued immediately and an alternative therapy initiated.

Hyperkalaemia
Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and in all patient treated for more than 7 days.

4.5 Interaction with other medicinal products and other forms of interaction

It is recommended that agents which affect haemostasis should be discontinued prior to enoxaparin therapy unless their use is essential. These agents include medications such as:

- systemic salicylates, acetylsalicylic acid and NSAIDS including ketorolac
- Dextran 40, ticlopidine, and clopidogrel.
- Systemic glucocorticoids
- thrombolytics and anticoagulants
- other anti-platelet agents including glycoprotein IIb/IIIa antagonists.

If the combination cannot be avoided, enoxaparin should be used with careful clinical and laboratory monitoring.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no evidence of teratogenic effect in animal studies. In humans, there is no evidence that enoxaparin sodium crosses the placenta barrier during the second trimester of pregnancy. There is no information available concerning the first and third trimesters.

As there are no adequate and well controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the physician has established a clear need.

The use of clexane 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 (1mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and foetal death. There have been isolated post-marketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see Section 4.5: Pregnant women with mechanical prosthetic heart valves and :Mechanical prosthetic heart valves).

Lactation

In lactating rats, the concentration of ^{35}S-enoxaparin sodium or its labelled metabolites in milk is very low.
It is not known whether unchanged exoxaparin sodium is excreted in human breast milk. The oral absorption of enoxaparin sodium is unlikely. However, as a precaution, lactating mothers receiving enoxaparin sodium should be advised to avoid breast-feeding.

4.7 Effects on ability to drive and use machines

Enoxaparin has no effect on the ability to drive and operate machines.

4.8 Undesirable effects

The adverse reactions observed in these clinical studies and reported in 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); very rare (< 1/10,000) or not known (cannot be estimated from available data). Post marketing adverse reactions are designated with a frequency 'not known'.

Haemorrhages
In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients[1],). Some of these cases have been fatal.
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 Section 4.4 and Section 4.5). The origin of the bleeding should be investigated and appropriate treatment instituted.

[1]In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by an haemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.

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

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

Thrombocytopenia and thrombocytosis

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

*: Platelet increased > 400 G/L

Other clinically relevant adverse reactions
These reactions are presented below, whatever the indications, by system organ class, frequency grouping and decreasing order of seriousness.

MedDRA system	All indications

organ class	
Immune system disorders	*Common:* Allergic reaction *Rare:* Anaphylactic / anaphylactoid reaction (see also post marketing experience)
Hepatobilary disorders	*Very common:* Hepatic enzymes increase (mainly transaminases **)
Skin and subcutaneous tissue disorders	*Common:* Urticaria, pruritus, erythema, *Uncommon:* Bullous dermatitis
General disorders and administration site conditions	*Common:* Injection site haematoma, injection site pain, other injection site reaction* *Uncommon:* Local irritation; skin necrosis at injection site
Investigations	*Rare:* Hyperkaliemia

*: such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction (NOS)
**: transaminases levels > 3 times the upper limit of normality

Post marketing experience

The following adverse reactions have been identified during post-approval use of Clexane. The adverse reactions are derived from spontaneous reports and therefore, the frequency is 'not known' (cannot be estimated from the available data).

- Immune System Disorders

- Anaphylactic/anaphylactoid reactions including shock.

- Nervous System Disorders

- Headache.

- Vascular Disorders

- Cases of spinal haematoma (or neuraxial haematoma) have been reported with the concurrent use of enoxaparin sodium as well as spinal/epidural anaesthesia or spinal puncture. These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see Section 4.5: Spinal/epidural anesthesia).

- Blood and Lymphatic System Disorders

- Haemorrhagic anaemia.
- Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see Section 4.5; Monitoring of platelet counts).
- Eosinophilia.

- Skin and subcutaneous disorders

- Cutaneous vasculitis, skin necrosis usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful).
  Treatment with enoxaparin sodium must be discontinued.
- Injection site nodules (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.
- Alopeica.

- Hepatobilary disorders

- Hepatocellular liver injury.
- Cholestatic liver injury.

- Musculoskeletal and connective tissue disorders

- Osteoporosis following long-term therapy (greater than 3 months).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Orally administered enoxaparin is poorly absorbed and even large oral doses should not lead to any serious

consequences. This may be checked by plasma assays of anti-Xa and anti-IIa activities.

Accidental overdose following parenteral or extracorporeal administration may produce haemorrhagic complications. These may be largely neutralised by slow intravenous injection of protamine.

The dose of protamine depends on the dose of enoxaparin sodium injected:

- 1 mg protamine neutralizes the anticoagulant effect of 1 mg of enoxaparin sodium, if enoxaparin sodium was administered in the previous 8 hours.
- An infusion of 0.5 mg protamine per 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 is never completely neutralised (maximum approximately 60%). *(See the prescribing information for protamine salts).*

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Enoxaparin is a low molecular weight heparin, with a mean molecular weight of approximately 4,500 daltons. In the in vitro purified system, enoxaparin has a high anti-Xa activity (approximately 100 IU/mg) and low anti-IIa or anti thrombin activity (approximately 28 IU/mg). These anticoagulant activities are mediated through anti-thrombin III (ATIII) resulting in anti-thrombotic activities in humans.

Beyond its anti-Xa activity, further anti-thrombotic 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 anti-thrombotic effect of enoxaparin.

At the recommended doses, enoxaparin does not influence bleeding time and global blood coagulation tests significantly, nor does it affect platelet aggregation or binding of fibrinogen to platelets.

CLINICAL EFFICACY/CLINICAL STUDIES

Treatment of unstable angina and non-Q-wave myocardial infarction

In a large multicenter 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 aspirin (100 to 325 mg once daily),either subcutaneous enoxaparin sodium 1 mg/kg every 12 hours or intravenous unfractionated heparin adjusted based on activated partial thromboplastin time (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. Enoxaparin sodium compared to heparin significantly decreased the incidence of recurrent angina, myocardial infarction and death, with a relative risk reduction of 16.2% at Day 14, sustained over the 30 day period. Furthermore, fewer patients in the enoxaparin sodium group underwent revascularization with either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) (15.8% relative risk reduction at Day 30).

Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)

In a large multicenter study, 20479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either enoxaparin sodium in a single 30-mg intravenous bolus plus a 1 mg/kg SC Enoxaparin dose followed by an SC injection of 1.0 mg/kg every 12 hours or intravenous unfractionated heparin adjusted based on activated partial thromboplastin time (aPTT) for 48 hours. All patients were also treated with aspirin for a minimum of 30 days. The enoxaparin 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 were given until hospital discharge or for a maximum of eight days (whichever came first).

4716 patients underwent percutaneous coronary intervention receiving antithrombotic support with blinded study drug. Therefore, for patients on enoxaparin, the PCI was to be performed on enoxaparin (no switch) using the regimen established in previous studies i.e. no additional dosing, if last SC administration given less than 8 hours before balloon inflation, IV bolus of 0.3 mg/kg enoxaparin, 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 re-infarction in the first 30 days after randomization [9.9 percent in the enoxaparin group, as compared with 12.0 percent in the unfractionated heparin group] with a 17 percent relative risk reduction (P<0.001). The treatment benefits of enoxaparin, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35 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 on the primary end point was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, type of fibrinolytic administered, and time to treatment with study drug. There was a significant treatment benefit of enoxaparin, as compared with unfractionated heparin, in patients who underwent percutaneous coronary intervention within 30 days after randomization (23 percent reduction in relative risk) or who were treated medically (15 percent reduction in relative risk, P = 0.27 for interaction).

The rate of the 30 day composite endpoint of death, myocardial re-infarction or ICH (a measure of net clinical benefit) was significantly lower (p<0.0001) in the enoxaparin group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favor of treatment with Clexane. The beneficial effect of enoxaparin on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period.

5.2 Pharmacokinetic properties

General characteristics
The pharmacokinetic parameters of enoxaparin sodium have been studied mainly 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 subcutaneous administration and after single intravenous administration.
The quantitative determination of anti-Xa and anti-IIa pharmacokinetic activities was conducted by validated amidolytic methods with specific substrates and an enoxaparin standard calibrated against the international standard for LMWHs (NIBSC).

Bioavailability:
The absolute bioavailability of enoxaparin sodium after subcutaneous injection, based on anti-Xa activity, is close to 100 %. Injection volume and dose concentration over the range 100-200mg/ml does not affect pharmacokinetic parameters in healthy volunteers.

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

Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges. Intra-patient and inter-patient variability is low. After repeated subcutaneous administration of 40mg once daily and 1.5mg/kg once daily regimens in healthy volunteers, the steady-state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single dose pharmacokinetics.

After repeated subcutaneous administration of the 1mg/kg twice daily regimen, the steady state is reached from day 3 to 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/ml, respectively.

Based on enoxaparin sodium pharmacokinetics, this difference in steady-state is expected within the therapeutic range.

Plasma anti-IIa activity after subcutaneous administration is approximately ten-fold lower than anti-Xa activity. The mean maximum anti-IIa activity is observed approximately 3 to 4 hours following subcutaneous injection of 40 mg (while it is not detectable at the 20 mg dose level when using conventional amidolytic method) and reaches 0.13 IU/ml and 0.19 IU/ml following repeated administration of 1mg/kg twice daily and 1.5mg/kg once daily, respectively.

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

Elimination and Metabolism:
Enoxaparin sodium is a low clearance drug with a mean anti-Xa plasma clearance of 0.74 L/h after a 1.5mg/kg 6-hour intravenous infusion.
Elimination appears monophasic with a half-life of about 4 hours after a single-subcutaneous dose to about 7 hours after repeated dosing. The anti-Xa activity is measurable in the plasma up to 24 hours after subcutaneous injection of 40 mg enoxaparin.

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

Characteristics in 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 Precautions: Haemorrhage in the Elderly, Dosage and Administration: Elderly and Pharmacokinetics: Renal impairment).

Renal impairment:
A linear relationship exists 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 50-80ml/min) and moderate (creatinine clearance 30-50ml/min) renal impairment after repeated subcutaneous 40mg once daily doses. In patients with severe renal impairment (creatinine clearance<30ml/min), the AUC at steady state is significantly increased on average by 65% after repeated subcutaneous 40mg once daily doses (see Precautions: Renal impairment and Dosage and Administration: Renal impairment).

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

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

Haemodialysis:
In a single study, elimination rate appeared similar but AUC was two fold higher than control population, after a single 0.25 or 0.50mg/kg intravenous dose.

5.3 Preclinical safety data

No further information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

Hypak SCF pre-filled syringes (Becton Dickinson) in packs of 10, containing 0.2ml or 0.4ml of solution.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

See "Posology and method of administration".

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/064/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 21st December 2006

Date of Last Renewal: 21st December 2011

10 DATE OF REVISION OF THE TEXT

April 2014