For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

THROMBIFLO
(Enoxaparin Sodium Injection I.P.)
Low molecular weight heparin

COMPOSITION
Per syringe:
Enoxaparin Sodium I.P. 20 mg, 40 mg & 60 mg
Water for Injection I.P. q.s. to 0.2 ml, 0.4 ml & 0.6 ml
Enoxaparin sodium starting material is porcine derived

PHARMACEUTICAL FORM
Sterile, pyrogen-free and injectable solution contained in ready-to-use prefilled syringes.

PHARMACO-THERAPEUTIC CLASS
Antithrombotic/Low Molecular Weight Heparin (B: blood, hematopoietic organs).

INDICATIONS

Solution for injection at 20 mg and 40 mg.
Prophylaxis of venous thromboembolic disease (prevention of blood clot formation in the veins), in particular after certain procedures.
Prevention of thrombus formation in the extracorporal circulation during hemodialysis.

Solution for injection at 60 mg.
Treatment of established deep vein thrombosis.
Treatment of unstable angina and non-Q- wave myocardial infarction during the acute stage, in combination with aspirin**.**

POSOLOGY AND METHOD OF ADMINISTRATION

1 mg (0.01ml) of enoxaparin corresponds approximately to 100 anti-Xa I.U. Enoxaparin should be injected by deep SUBCUTANEOUS ROUTE in prophylactic and curative treatment and by INTRAVASCULAR ROUTE during haemodialysis.
Do not inject intramuscularly.

Subcutaneous administration technique : The prefilled syringes are ready-to-use. **The air bubble from the syringe should not be expelled before the injection.** The subcutaneous injection should preferably be made when the patient is lying down. Enoxaparin is administered in the subcutaneous cellular tissue of the anterolateral or posterolateral abdominal wall, alternately on the left and the right side. The injection itself consists in introducing the needle perpendicularly and not tangentially, throughout its entire length into a fold of skin held between the thumb and index finger. The skin fold should be held throughout the injection.

Prophylaxis of venous thrombosis : In the case of a surgery with a moderate thombogenic risk and when patients do not present high thrombo-embolism risk, the recommended dosage is 20 mg (0.2 ml) once daily by a single subcutaneous injection. In the case of a surgery with a high thombogenic risk(hip and knee surgery) and /or in patients with a high risk of thrombo-embolism, the dosage should be 40 mg (0.4 ml) once daily by a single subcutaneous injection. In general surgery, the first injection should be given 2 hours before the surgical procedure. In orthopaedic surgery, the first injection is to be given 12 hours pre- operatively. A higher prophylactic dosage may be envisaged when the risk of thrombo-embolism linked to the type of surgery and/or to the patient's history is increased. Enoxaparin treatment is usually prescribed for an average period of 7 to 10 days. Longer treatment duration may be appropriate in certain cases and the treatment should be continued for as long as there is a risk of venous thrombo- embolism and until the patient is ambulatory.

Prevention of extra corporal thrombus during haemodialysis :
The recommended dose is 1 mg/kg. Enoxaparin should be introduced in 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; in the event fibrin rings are found, a further dose of 0.5 to 1 mg/kg may be given.

Treatment of established deep vein thrombosis :
A dose of 1 mg/kg should be given subcutaneously every 12 hours. The duration of the treatment should not exceed a period of 10 days.

Treatment of unstable angina and non-Q-wave myocardial infarction :
A dose of 1 mg/kg should be given subcutaneously every 12 hours. The recommended treatment should be prescribed for a period of 2 to 8 days, until clinical stabilization of the patient. Enoxaparin should be administered concurrently with aspirin (100 to 325 mg daily per oral route).

Elderly: No dosage adjustment is necessary in preventive therapy. In curative therapy measurement of anti-Xa activity is recommended.

Children: Enoxaparin in not recommended for children.

Renal Impairment:

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

Dosage Adjustments For Therapeutic Dosage Ranges:

Standard dosing	Severe renal impairment
1 mg/kg twice daily	1 mg/kg once daily
1.5 mg/kg once daily	1 mg/kg once daily
Dosage adjustments for prophylactic dosage ranges	
Standard dosing	Severe renal impairment
40 mg once daily	20 mg once daily
20 mg once daily	20 mg once daily

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

Moderate and mild renal impairment: Although no dosage adjustments are recommended in patients with moderate renal impairment (Creatinine clearance 30-50 ml/min) or mild renal impairment (creatinine clearance 50-80 ml/min), careful clinical monitoring is advised.

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

Patients under 40 kg and over 100 kg weight: Particular clinical surveillance is necessary in order to adjust dosage if necessary. In all cases, strictly follow the Physician's prescription.

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;

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

SPECIAL WARNINGS AND 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 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.

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.

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. 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.

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.

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.
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.
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.

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.

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.

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.

Hyperkalemia
Heparins can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-

existing metabolic acidosis, taking medicinal products known to increase potassium. 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.

DRUG INTERACTION

Concomitant use not recommended:

Medicinal products affecting hemostasis
It is recommended that some agents which affect hemostasis 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.

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 (cardioprotection), 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.

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 teratogenicity. 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.
If an epidural anaesthesia is planned, it is recommended to withdraw enoxaparin sodium treatment before.

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. Enoxaparin 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Enoxaparin sodium has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

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 treatment of DVT with or without PE, patients receiving enoxaparin sodium were treated with either a 100 IU/kg (1 mg/kg) SC dose every 12 hours or a 150 IU/kg (1.5 mg/kg) SC dose once a day. In the clinical studies for treatment of unstable angina and non-Q-wave myocardial infarction, doses were 100 IU/kg (1 mg/kg) SC every 12 hours, and in the clinical study for treatment of acute STEMI enoxaparin

sodium regimen was a 3,000 IU (30 mg) IV bolus followed by 100 IU/kg (1 mg/kg) SC every 12 hours.

In clinical studies, haemorrhages, thrombocytopenia and thrombocytosis were the most commonly reported reactions.

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*
Rare: Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia.

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.

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*
Rare: 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 injection site

Investigations
Rare: Hyperkalaemia*.
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.

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 gastro-intestinal 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] *Common:* **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.

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 properties**

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

Pharmacodynamic effects

Enoxaparin is a LMWH with a mean molecular weight of approximately 4,500 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 anti thrombin activity (approximately 28 IU/mg), with a ratio of 3.6. These anticoagulant activities are mediated through anti-thrombin III (ATIII) resulting in anti-thrombotic activities in humans.

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

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

When used as prophylactic treatment, enoxaparin sodium does not significantly affect the aPTT. When used as curative treatment, aPTT can be prolonged by 1.5-2.2 times the control time at peak activity.

Clinical efficacy and safety

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 multicenter, 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 multicenter, 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 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 acetylsalicylic acid (100 to 325 mg once daily), either SC 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 multicenter study, 20,479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either enoxaparin sodium 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).

4,716 patients underwent percutaneous coronary intervention receiving antithrombotic support with blinded study drug. 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 re-infarction in the first 30 days after randomization [9.9 percent in the enoxaparin sodium 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 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 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 sodium, 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 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 sodium 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 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 activity and also by anti-IIa activity, at the recommended dosage ranges after single and repeated SC administration and after single IV administration. The quantitative determination of anti-Xa and anti-IIa pharmacokinetic activities was conducted by validated amidolytic methods.

Absorption
The absolute bioavailability of enoxaparin sodium after SC injection, based on anti-Xa activity, is close to 100%. Different doses and formulations and dosing regimens can be used. The mean maximum plasma anti-Xa activity level is observed 3 to 5 hours after SC injection and achieves approximately 0.2, 0.4, 1.0 and 1.3 anti-Xa IU/ml following single SC administration of 2,000 IU, 4,000 IU, 100 IU/kg and 150 IU/kg (20 mg, 40 mg, 1 mg/kg and 1.5 mg/kg) doses, respectively.

A 3,000 IU (30 mg) IV bolus immediately followed by a 100 IU/kg (1 mg/kg) SC every 12 hours provided initial maximum anti-Xa activity level of 1.16 IU/ml (n=16) and average exposure corresponding to 88% of steady-state levels. Steady-state is achieved on the second day of treatment.

After repeated SC administration of 4,000 IU (40 mg) once daily and 150 IU/kg (1.5 mg/kg) once daily regimens in healthy volunteers, the steady-state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. After repeated SC administration of the 100 IU/kg (1 mg/kg) twice daily regimen, the steady-state is reached from day 3 to 4 with mean exposure about 65% higher than after a single dose and mean maximum and trough anti-Xa activity levels of about 1.2 and 0.52 IU/ml, respectively.

Injection volume and dose concentration over the range 100-200 mg/ml does not affect pharmacokinetic parameters in healthy volunteers.
Enoxaparin sodium pharmacokinetics appears to be linear over the recommended dosage ranges.
Intra-patient and inter-patient variability is low. Following repeated SC administration no accumulation takes place.

Plasma anti-IIa activity after SC administration is approximately ten-fold lower than anti-Xa activity. The mean maximum anti-IIa activity level is observed approximately 3 to 4 hours following SC injection and reaches 0.13 IU/ml and 0.19 IU/ml following repeated administration of 100 IU/kg (1 mg/kg) twice daily and 150 IU/kg (1.5 mg/kg) once daily, respectively.

Distribution
The volume of distribution of enoxaparin sodium anti-Xa activity is about 4.3 litres and is close to the blood volume.

Biotransformation
Enoxaparin sodium is primarily metabolized 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.

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

Renal impairment
A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 ml/min) and moderate (creatinine clearance 30-50 ml/min) renal impairment after repeated SC 4,000 IU (40 mg) once daily doses. In patients with severe renal impairment (creatinine clearance <30 ml/min), the AUC at steady state is significantly increased on average by 65% after repeated SC 4,000 IU (40 mg) once daily doses.

Haemodialysis
Enoxaparin sodium pharmacokinetics appeared similar than control population, after a single 25 IU, 50 IU or 100 IU/kg (0.25, 0.50 or 1.0 mg/kg) IV dose however, AUC was two-fold higher than control.

Weight
After repeated SC 150 IU/kg (1.5 mg/kg) once daily dosing, mean AUC of anti-Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while maximum plasma anti-Xa activity level is not increased. There is a lower weight-adjusted clearance in obese subjects with SC dosing.
When non-weight adjusted dosing was administered, it was found after a single-SC 4,000 IU (40 mg) dose, that anti-Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects.

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 *no clastogenic* activity based on an *in vitro* human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test.
Studies conducted in pregnant rats and rabbits at SC doses of enoxaparin sodium up to 30 mg/kg/day did not reveal any evidence of teratogenic effects or foetotoxicity. 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.

EXPIRY DATE
Do not use later than the date of expiry.

DIRECTION
Swallow whole tablet, do not crush or chew.

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not more than 30°C, Protected from light and moisture. Keep out of reach of children.

MARKETED BY

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