Parinox®

Enoxaparin sodium

FORMS AND PRESENTATION

Parinox® 20: 2,000IU (20mg)/0.2ml, Solution for injection: Box of 1 prefilled syringe (PFS).
Parinox® 40: 4,000IU (40mg)/0.4ml, Solution for injection: Box of 1 prefilled syringe (PFS).
Parinox® 60: 6,000IU (60mg)/0.6ml, Solution for injection: Box of 1 prefilled syringe (PFS).
Parinox® 80: 8,000IU (80mg)/0.8ml, Solution for injection: Box of 1 prefilled syringe (PFS).

COMPOSITION

Parinox® 20: Each PFS contains Enoxaparin sodium 20 mg (equivalent to 2,000IU anti-Xa activity) in 0.2 ml water for injection.
Parinox® 40: Each PFS contains Enoxaparin sodium 40 mg (equivalent to 4,000IU anti-Xa activity) in 0.4 ml water for injection.
Parinox® 60: Each PFS contains Enoxaparin sodium 60 mg (equivalent to 6,000IU anti-Xa activity) in 0.6 ml water for injection.
Parinox® 80: Each PFS contains Enoxaparin sodium 80 mg (equivalent to 8,000IU anti-Xa activity) in 0.8 ml water for injection.
Excipients: water for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent, heparin group, ATC code: B01AB05
Enoxaparin is a low molecular weight heparins (LMWH) with a mean molecular weight of approximately 4,500 daltons, in which the antithrombotic and anticoagulant activities of standard heparin have been dissociated. 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.

Pharmacokinetic properties

Absorption

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

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: when the renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium compared to younger patients.

Hepatic impairment: when treated with enoxaparin sodium 4,000 IU (40 mg) once daily, the decrease in maximum anti-Xa activity is mainly attributed to a decrease in ATIII level secondary to a reduced synthesis of ATIII in patients with hepatic impairment.

Renal impairment: anti-Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 mL/min), moderate (creatinine clearance 30-50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment after repeated SC 4,000 IU (40 mg) once daily doses.

Weight: 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.

INDICATIONS

Parinox® 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.
• Prophylaxis of venous thromboembolic disease in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infections 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.
• Prevention of thrombus formation in extra corporeal circulation during haemodialysis.
• 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).

CONTRAINDICATIONS

–Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including other LMWH or to any of the excipients listed
– 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.

PRECAUTIONS

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).

History of HIT (>100 days): Use of enoxaparin sodium in patients with a history of HIT within the past 100 days or in the presence of circulating antibodies is contraindicated. Circulating antibodies may persist several years.

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 Parinox® 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 and the patient should inform his primary care physician. In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50 % of the initial value), Parinox® treatment must be immediately discontinued and the patient switched to another non-heparin anticoagulant alternative treatment.

Haemorrhage: If bleeding occurs, the origin of the haemorrhage should be investigated and appropriate treatment instituted. Parinox®, 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, and concomitant use of medications affecting haemostasis.

Spinal/Epidural anaesthesia or lumbar puncture: It must not be performed within 24 hours of administration of Parinox® 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. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of enoxaparin sodium is low. For patients with creatinine clearance [15-30 mL/minute], additional considerations are necessary because elimination of enoxaparin sodium is more prolonged.

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.

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: Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin sodium for thromboprophylaxis. Some of the cases were pregnant women in whom thrombosis led to maternal and foetal death.

Elderly: 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: The risk of bleeding is increased due to the increase in exposure of enoxaparin sodium. 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). 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 men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients.
Obese Patients: They 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 should be observed carefully for signs and symptoms of thromboembolism.
Hyperkalaemia: Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, preexisting metabolic acidosis, taking medicinal products known to increase potassium. Plasma potassium should be monitored regularly especially in patients at risk.
Effects on ability to drive and use machines
Enoxaparin sodium has no or negligible influence on the ability to drive and use machines.
PREGNANCY AND LACTATION
Pregnancy: In humans, there is no evidence that enoxaparin crosses the placental barrier during the second and third trimester of pregnancy. Parinox® should be used during pregnancy only if the physician has established a clear need. Pregnant women receiving Parinox® should be carefully monitored for evidence of bleeding or excessive anticoagulation and should be warned of the haemorrhagic risk. 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. The oral absorption of enoxaparin sodium is unlikely. Parinox® can be used during breastfeeding.
DRUG INTERACTIONS
Concomitant use not recommended:
Medicinal products affecting haemostasis
If the combination is indicated, Parinox® 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:
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: may be administered concurrently with Parinox® under careful clinical and laboratory monitoring.
ADVERSE EFFECTS
Adverse effects are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10,000) or not known (cannot be estimated from available data).
Blood and the lymphatic system disorders: haemorrhage, haemorrhagic anaemia, thrombocytopenia, thrombocytosis (common); eosinophilia (rare).
Immune system disorders: allergic reaction (common); anaphylactic/anaphylactoid reactions including shock (rare).
Nervous system disorders: headache (common).
Vascular disorders: spinal or neuraxial haematoma (rare).
Hepato-biliary disorders: hepatic enzyme increases (mainly transaminases >3 times the upper limit of normality) (very common); hepatocellular liver injury (uncommon); cholestatic liver injury (rare).
Skin and subcutaneous tissue disorders: urticaria, pruritus, erythema (common); bullous dermatitis (uncommon); alopecia, cutaneous vasculitis, skin necrosis (rare).
Musculoskeletal, connective tissue and bone disorders: osteoporosis (rare).
General disorders and administration site conditions: injection site haematoma, injection site pain, other injection site reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction) (common); local irritation, skin necrosis at injection site (uncommon).
Investigations: hyperkalaemia (rare).
DOSAGE AND ADMINISTRATION
Posology
- moderate risk of thromboembolism: the recommended dose is 2,000 IU (20 mg) once daily by subcutaneous (SC) injection.
- 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.
Prophylaxis of venous thromboembolism in medical patients: The recommended dose is 4,000 IU (40 mg) once daily by SC injection. Treatment with Parinox® 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: Parinox® 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 high venous thromboembolism (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. Parinox® treatment is prescribed for an average period of 10 days. Oral anticoagulant therapy should be initiated when appropriate.
Prevention of thrombus formation during haemodialysis: The recommended dose is 100 IU/kg (1 mg/kg). 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, Parinox® 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.
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 Parinox® 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 is a single 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 (maximum 10,000 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), Parinox® should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy.
• For patients managed with PCI, if the last dose of Parinox® 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) Parinox® should be administered. 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 solution, using Parinox® 60 prefilled 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 Parinox® 60 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.
Elderly: 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).
• Severe renal impairment: the recommended dosage adjustments do not apply to the haemodialysis indication.
• Moderate and mild renal impairment: no dose adjustment is recommended and careful clinical monitoring is advised.
Method of administration
Parinox® 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 extra corporeal circulation during haemodialysis, it is administered through the arterial line of a dialysis circuit.
• SC injection technique: injection should be made preferably when the patient is lying down. Parinox® 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. 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 only, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection. Parinox® should be administered through an IV line. It should not be mixed or coadministered with other medications. To avoid the possible mixture of Parinox® 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 Parinox® to clear the port of drug. Parinox® may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.
OVERDOSAGE
Signs and symptoms
Accidental overdose with enoxaparin sodium after IV 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 Parinox® was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 100 IU (1 mg) of Parinox® 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%).
STORAGE CONDITIONS
Store below 25°C.
Keep in original pack in intact conditions.
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Marketing Authorization Holder & Manufacturer
Benta S.A.L. - Lebanon

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