Abbreviated Prescribing Information

PRESENTATION: Enoxaparin sodium is a biological substance obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa**.** Per pre-filled syringes of enoxaparin sodium 2000 IU anti-Xa for 0.2 ml, 4000 IU anti-Xa for 0.4 ml, 6000 IU anti-Xa for 0.6 ml, 8000 IU anti-Xa for 0.8 ml & 10000 IU anti-Xa for 1 ml equivalent to 20 mg, 40 mg, 60 mg, 80 mg and 100 mg respectively. For the full list of excipients, see full SmPC - **INDICATIONS:** (1) Prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients, in particular those undergoing orthopedic or general surgery including cancer surgery. (2) 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. (3) Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery. (4) Prevention of thrombus formation in extra corporeal circulation during hemodialysis. (5) Acute coronary syndrome: (a) Treatment of unstable angina and Non-ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid. (b) Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI). **DOSAGE AND ADMINISTRATION:** Prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients' Individual thromboembolic risk for patients can be estimated using validated risk stratification model. (a) In patients at moderate risk of thromboembolism, the recommended dose of enoxaparin sodium is 2000 IU (20 mg) once daily by subcutaneous (SC) injection. Preoperative initiation (2 hours before surgery) of enoxaparin sodium 2 000 IU (20 mg) was proven effective and safe in moderate risk surgery. In moderate risk patients, enoxaparin sodium treatment should be maintained for a minimal period of 7-10 days whatever the recovery status (e.g. mobility). Prophylaxis should be continued until the patient no longer has significantly reduced mobility. (b) In patients at high risk of thromboembolism, the recommended dose of enoxaparin sodium is 4000 IU (40 mg) once daily given by SC injection preferably started 12 hours before surgery. If there is a need for earlier than 12 hours enoxaparin sodium preoperative prophylactic initiation (e.g. high risk patient waiting for a deferred orthopedic surgery), the last injection should be administered no later than 12 hours prior to surgery and resumed 12 hours after surgery. (c) For patients who undergo major orthopedic surgery an extended thromboprophylaxis up to 5 weeks is recommended. (d) For patients with a high venous thromboembolism (VTE) risk who undergo abdominal or pelvic surgery for cancer an extended thromboprophylaxis up to 4 weeks is recommended. (2) Prophylaxis of venous thromboembolism in medical patients: The recommended dose of enoxaparin sodium is 4 000 IU (40 mg) once daily by SC injection. Treatment with enoxaparin sodium is prescribed for at least 6 to 14 days whatever the recovery status (e.g. mobility). The benefit is not established for a treatment longer than 14 days. (3) Treatment of DVT and PE: Enoxaparin sodium can be administered SC either as a once daily injection of 150 IU/kg (1.5 mg/kg) or as twice daily injections of 100 IU/kg (1 mg/kg). The regimen should be selected by the physician based on an individual assessment including evaluation of the thromboembolic risk and of the risk of bleeding. The dose regimen of 150 IU/kg (1.5 mg/kg) administered once daily should be used in uncomplicated patients with low risk of VTE recurrence. The dose regimen of 100 IU/kg (1 mg/kg) administered twice daily should be used in all other patients such as those with obesity, with symptomatic PE, cancer, recurrent VTE or proximal (vena iliaca) thrombosis. Enoxaparin sodium treatment is prescribed for an average period of 10 days. Oral anticoagulant therapy should be initiated when appropriate (see full SmPC for more details). (4) Prevention of thrombus formation during hemodialysis: The recommended dose is 100 IU/kg (1 mg/kg) of enoxaparin sodium. For patients with a high risk of hemorrhage, 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 hemodialysis, enoxaparin sodium should be introduced into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 50 IU to 100 IU/kg (0.5 to 1 mg/kg) may be given. No data are available in patients using enoxaparin sodium for prophylaxis or treatment and during hemodialysis sessions. (5) Acute coronary syndrome: treatment of unstable angina and NSTEMI and treatment of acute STEMI: (a) For treatment of unstable angina and NSTEMI, the recommended dose of enoxaparin sodium is 100 IU/kg (1 mg/kg) every 12 hours by SC injection administered in combination with antiplatelet therapy. Treatment should be maintained for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days. Acetylsalicylic acid is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in acetylsalicylic acid-naive patients) and a maintenance dose of 75–325 mg/day long-term regardless of treatment strategy. (b) For treatment of acute STEMI, the recommended dose of enoxaparin sodium is a single intravenous (IV) bolus of 3000 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 10000 IU (100 mg) for each of the first two SC doses). Appropriate antiplatelet therapy such as oral acetylsalicylic acid (75 mg to 325 mg once daily) should be administered concomitantly unless contraindicated. The recommended duration of treatment is 8 days or until hospital discharge, whichever comes first. When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific), enoxaparin sodium should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. (c) For dosage in patients ≥ 75 years of age, see full SmPC o for patients managed with PCI, if the last dose of enoxaparin sodium SC was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last SC administration was given more than 8 hours before balloon inflation, an IV bolus of 30 IU/kg (0.3 mg/kg) enoxaparin sodium should be administered. For pediatric populations, elderly patients, hepatic impairment patients and renal impaired patients - See full SmPC. **Method of administration:** Clexane 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. (a) For acute STEMI, treatment is to be initiated with a single IV bolus injection immediately followed by a SC injection. (b) For the prevention of thrombus formation in the extra corporeal circulation during hemodialysis, it is administered through the arterial line of a dialysis circuit. The pre-filled disposable syringe is ready for immediate use. For full techniques of administration see full SmPC. **CONTRA-INDICATIONS:** Enoxaparin sodium is contraindicated in patients with: (1) Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including other low molecular weight heparins (LMWH) or to any of the excipients listed in full SmPC (2) History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (3) Active clinically significant bleeding and conditions with a high risk of hemorrhage, including recent hemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities; (4) Spinal or epidural anesthesia or loco-regional anesthesia when enoxaparin sodium is used for treatment in the previous 24 hours. - See full SmPC. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** for full list of special warnings and precautions, See the Full SmPC. 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. See full SmPC. Hemorrhage: As with other anticoagulants, bleeding may occur at any site. If bleeding occurs, the origin of the hemorrhage 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 hemostasis, history of peptic ulcer, recent ischemic stroke, severe arterial hypertension, recent diabetic retinopathy, neuro- or ophthalmologic surgery, concomitant use of medications affecting hemostasis. 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 anesthesia or lumbar puncture Spinal/epidural anesthesia or lumbar puncture must not be performed within 24 hours of administration of enoxaparin sodium at therapeutic doses – See Full SmPC. There have been cases of neuraxial hematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anesthesia or spinal puncture procedures resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 4000 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 hemostasis 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 anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of enoxaparin sodium – See Full SmPC. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of enoxaparin sodium is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. For patients with creatinine clearance [15-30 ml/minute], additional considerations are necessary because elimination of enoxaparin sodium is more prolonged – See Full SmPC. Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/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. For full list of warnings and precautions as: Skin necrosis / cutaneous vasculitis, Percutaneous coronary revascularization procedures, Acute infective endocarditis, Elderly, Renal impairment, Hepatic impairment, Low weight, Obese Patients, Hyperkalemia, Traceability, see full SmPC. Mechanical prosthetic heart valves, 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 fetal 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. See Full SmPC. **DRUG INTERACTIONS:** Concomitant use not recommended: (1) 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: (a) Systemic salicylates, acetylsalicylic acid at anti-inflammatory doses, and NSAIDs including ketorolac (b) Other thrombolytics (e.g. alteplase, reteplase, streptokinase, tenecteplase, urokinase) and anticoagulants, See Full SmPC. Concomitant use with caution: The following medicinal products may be administered with caution concomitantly with enoxaparin sodium: (a) Other medicinal products affecting hemostasis 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 (b) 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. For full details, See Full SmPC. **Fertility, pregnancy, and lactation:** Pregnancy: In humans, there is no evidence that enoxaparin crosses the placental barrier during the second and third trimester of pregnancy. There is no information available concerning the first trimester. Animal studies have not shown any evidence of fetotoxicity or teratogenicity (see section 5.3). Animal data have shown that enoxaparin passage through the placenta is minimal. 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 hemorrhagic risk. Overall, the data suggest that there is no evidence for an increased risk of hemorrhage, 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 anesthesia 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. Clexane 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. (1) There are currently not enough relevant clinical data to evaluate possible teratogenic or fetotoxic effects of enoxaparin when the drug is administered at curative doses throughout the entire pregnancy. Therefore, as a precautionary measure, enoxaparin should preferably not be administered at curative doses during throughout the entire pregnancy. Epidural or spinal anesthesia must never be given with curative LMWH treatment. (2) Prophylactic enoxaparin treatment during the 2nd and 3rd trimesters should only be considered if necessary. If epidural anesthesia is planned, prophylactic heparin treatment should be interrupted whenever possible at the latest within 12 hrs. before anesthesia. (3) Since gastrointestinal absorption by neonates is unlikely in principle, treatment with enoxaparin is not contraindicated in breastfeeding women. See full SmPC. **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 orthopedic 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, hemorrhages, thrombocytopenia, and thrombocytosis were the most commonly reported reactions, for full details, see full SmPC. **OVERDOSAGE:** Signs and symptoms: Accidental overdose with enoxaparin sodium after IV, extracorporeal or SC administration may lead to hemorrhagic 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: (a) 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. (b) 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. (c) 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). See full SmPC. Further details and information are available on the full SmPC - **MARKETING AUTHORIZATION HOLDER:** Sanofi-Aventis france, 82, avenue Raspail 94250, gentilly, france. marketing authorisation number(s):- For further information kindly refer to full SmPC: dated March 2017.