**Clexane – KSA API**

**Abbreviated Prescribing Information**

**PRESENTATION:** Per syringe of enoxaparin sodium 2 000 IU anti-Xa for 0.2 ml, 4 000 IU anti-Xa for 0.4 ml, 6 000 IU anti-Xa for 0.6 ml & 8 000 IU anti-Xa for 0.8 ml equivalent to 20 mg, 40 mg, 60 mg & 80 mg respectively. **INDICATIONS:** (1) Prophylaxis of venous thromboembolic disease in moderate to high risk surgery, (2) Prevention of clotting in the extracorporeal circulation during hemodialysis (3) Prophylaxis of deep vein thrombosis in patients who are bedridden due to acute medical illness including (a) heart failure (NYHA class III or IV) (b) acute respiratory failure (c) an episode of acute infection or acute rheumatic disorder associated with at least one other venous thromboembolic risk factor (4) Curative treatment for established deep vein thrombosis, with or without pulmonary embolism, without signs of clinical seriousness excluding pulmonary emboli likely to require treatment with a thrombolytic agent or surgery (5) Treatment of unstable angina and acute non-Q-wave myocardial infarction, administered concurrently with aspirin (6) Treatment of acute ST-segment elevation myocardial infarction in combination with a thrombolytic agent in patients eligible or not for subsequent Percutaneous Coronary Intervention (PCI). **DOSAGE AND ADMINISTRATION:** Subcutaneous route (except for patients on hemodialysis). These presentations are for use in adults. Clexane is not intended for intramuscular administration. 1 ml of solution for injection is equivalent to approximately 10 000 IU anti-Xa of enoxaparin. Subcutaneous injection technique: The pre-filled syringe is ready for immediate use; no air should be expelled before administering the injection. Subcutaneous injection should be performed, preferably with the patient in the supine position. The injection should be given in the subcutaneous tissue, alternating between the left and right anterolateral and posterolateral abdominal walls. The whole length of the needle should be introduced vertically, not from the side, into a skin fold held between the thumb and index finger. This skin fold should not be released until the injection is complete. Regular monitoring of the platelet count is essential throughout the entire treatment due to the risk of heparin-induced thrombocytopenia (HIT). (1)Prophylaxis treatment of venous thromboembolic disease in surgery: As a general rule, these recommendations apply to surgical interventions carried out under general anesthesia. For spinal and epidural anesthesia techniques, the benefit of a preoperative injection should be weighed against the theoretically increased risk of spinal hematoma. Administration schedule: 1 injection daily. Dose administered: The dose should be determined based on the individual risk related to the patient and the type of surgery. (a) Surgery involving moderate thrombogenic risk: In surgery involving moderate thrombogenic risk and in patients who are not at high risk of thromboembolism, effective prevention is achieved by daily injection of 2 000 IU anti-Xa (0.2 ml). The studied dosage regimen involves administration of the 1st injection 2 hours before surgery. (b) Surgery involving high thrombogenic risk: (i) Hip and knee surgery: The dosage is 4 000 IU anti-Xa (0.4 ml) injected once daily. The studied dosage regimen involves either the 1st injection of 4 000 IU anti-Xa (total dose) 12 hours before surgery or a first injection of 2 000 IU anti-Xa (half dose) 2 hours before surgery. (ii) Other situations: When there appears to be an increased risk of venous thromboembolism due to the type of surgery (particularly cancer surgery) and/or due to the patient (particularly history of venous thromboembolism), administering a prophylactic dose identical to that for high-risk orthopedic surgery, e.g. hip or knee surgery, can be considered. Duration of treatment: Treatment with LMWH should be maintained, along with the usual method of compression stocking support of the legs, until the patient is fully and actively ambulatory; In general surgery, the duration of LMWH treatment must be less than 10 days, unless there is a patient-specific risk of venous thromboembolism; The therapeutic benefit of prophylactic treatment consisting of an injection of 4 000 IU anti-Xa/day of enoxaparin for 4-5 weeks after hip surgery has been established. If the patient is still at risk of venous thromboembolism after the recommended treatment duration, continued prophylactic therapy must be considered, particularly by administration of oral anticoagulants. The clinical benefit, however, of long-term treatment with LMWHs or oral anticoagulants has not yet been evaluated. (2) Prevention of clotting in the extracorporeal circulation / Hemodialysis: Intravascular route (in the arterial line of the dialysis circuit). In patients undergoing repeated hemodialysis sessions, prevention of clotting in the extrarenal purification system is obtained by injecting an initial dose of 100 IU anti-Xa /kg in the arterial line of the dialysis circuit at the beginning of the session. This dose, administered as a single intravascular bolus injection, is only suitable for hemodialysis sessions of 4 hours or less. It may be adjusted subsequently given high inter- and intra-individual variability. The maximum recommended dose is 100 IU anti-Xa/kg. In hemodialysis patients at high risk of hemorrhage (particularly pre- and post-operative dialysis) or with active hemorrhage, dialysis sessions may be carried out using a dose of 50 IU anti-X /kg (double vascular access) or 75 IU anti-Xa /kg (single vascular access). (3) Prophylactic treatment in the medical setting: The dose is 40 mg, i.e. 4 000 IU anti-Xa/0.4 ml, administered once daily by subcutaneous injection. Duration of treatment: It has been demonstrated that treatment is beneficial for between 6-14 days. To date, no efficacy and safety data are available concerning prophylaxis for more than 14 days. If the risk of venous thromboembolism persists, continued prophylactic treatment, particularly with oral anticoagulants, must be considered. (4) Intravenous (bolus) injection technique. Use of the Clexane 30 000 IU anti-Xa/3ml multiple-dose vial for the treatment of ST-segment elevation myocardial infarction: Treatment is initiated with an IV bolus injection, immediately followed by a subcutaneous injection. The initial dose of 3 000 IU, i.e. 0.3 ml, is to be drawn from the multiple-dose vial using a graduated 1 ml syringe (insulin syringe). This dose of enoxaparin should be injected intravenously. It should not be mixed or co-administered with other medications. In order to eliminate any traces of another drug, and thus avoid the possible mixture of enoxaparin with other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of enoxaparin sodium. Enoxaparin may be safely administered with a normal saline solution (0.9%) or 5% dextrose in water. In the hospital setting, the multiple-dose vial is then used to draw the following doses: (a) the dose required for the first SC injection of 100 IU/kg, given at the same time as the IV bolus, then for the subsequent SC injections of 100 IU/kg, to be repeated every 12 hours,(b) the 30 IU/kg dose for IV bolus injection if a subsequent percutaneous coronary intervention is

carried out. (5) Curative treatment of deep vein thrombosis (DVT), with or without pulmonary embolism, without signs of clinical seriousness: Any suspected DVT should be quickly confirmed by the appropriate examinations. Administration schedule: Twice daily injections at 12-hour intervals. Dose administered: The dose per injection is 100 IU anti-Xa/kg. LMWH dosage has not been evaluated in terms of body weight in patients weighing more than 100 kg or less than 40 kg. The efficacy of LMWH treatment may be slightly lower in patients weighing more than100 kg, and the risk of hemorrhage may be higher in patients weighing less than 40 kg. Special clinical monitoring must be carried out in these patients. Treatment duration in DVT patients: Treatment with LMWH should be quickly replaced by oral anticoagulant therapy, unless contraindicated. Treatment duration with LMWH should not exceed 10 days, including the time needed to reach the required oral anticoagulant effect, except when this is difficult to achieve. Oral anticoagulant treatment should therefore be initiated as soon as possible. (6) Curative treatment of unstable angina/non-Q-wave MI: A dose of 100 IU anti-Xa /kg of enoxaparin is administered by SC injection twice daily at 12-hour intervals, in combination with aspirin (recommended doses: 75-325 mg orally, following a minimum loading dose of 160 mg). The recommended duration of treatment is about 2-8 days, until clinical stabilization is achieved. (7) Treatment of acute ST-segment elevation MI in combination with a thrombolytic agent in patients eligible or not for a subsequent percutaneous coronary intervention: An initial IV bolus injection of 3 000 anti-Xa IU followed by an SC injection of 100 anti-Xa IU/kg within 15 minutes, then every 12 hours (a maximum of 10 000 anti-Xa IU for the 1st 2 SC doses). The 1st dose of enoxaparin should be administered at any time between 15 minutes before and 30 minutes after the start of thrombolytic treatment (whether fibrin specific or non-fibrin specific). The recommended duration of treatment is 8 days, or until the patient is discharged from hospital, if hospitalization is less than 8 days. Concomitant Treatment: Administration of aspirin must be instituted as soon as possible after symptoms appear, and maintained at a dosage of between 75 mg and 325 mg daily for at least 30 days, unless otherwise indicated. Patients managed by percutaneous coronary intervention: (a) If the last SC injection of enoxaparin was given less than 8 hours before balloon inflation, no additional dosing is necessary. (b) If the last SC injection was given more than 8 hrs before balloon inflation, an IV bolus of 30 anti-Xa IU/kg of enoxaparin should be administered. In order to optimize the accuracy of the volumes to be injected, it is recommended to dilute the drug to 300 IU/ml (i.e. 0.3 ml of enoxaparin diluted in 10 ml). Patients aged 75 years and over: In patients aged 75 years and over treated for acute ST-segment elevation MI, the initial IV bolus injection should not be administered. An SC dose of 75 anti-Xa IU/kg every 12 hrs should be administered (maximum of 7500 anti-Xa IU for the 1st 2 injections only). - See full SmPC. **CONTRA-INDICATIONS:** This medicinal product must not be used in the following situations: (1) hypersensitivity to enoxaparin, heparin or its derivatives, including other LMWHs; (2) history of serious type II heparin-induced thrombocytopenia (HIT), whether caused by unfractionated or low molecular weight heparin (see Precautions for use); (3) bleeding or tendency to bleed related to impaired hemostasis (a possible exception to this contraindication may be disseminated intravascular coagulation, when not related to heparin treatment – see Precautions for use); (4) organic lesion likely to bleed; (5) clinically significant active bleeding; (6) intracerebral hemorrhage; (7) As no relevant data is available, in severe renal failure (decreased as creatinine clearance around 30 ml/min as estimated by the Cockcroft formula), except in the particular case of dialysis patients. In patients with severe renal failure, unfractionated heparin should be given. For an accurate estimation using the Cockcroft formula, it is necessary to use a recent body weight measurement; (7) Spinal or epidural anesthesia must never be performed in patients under curative LMWH treatment. This medicinal product is generally not recommended in the following situations: (1) acute, extensive ischemic stroke, with or without impaired consciousness. If the stroke is caused by embolism, enoxaparin must not be administered for 72 Hrs following the event. The efficacy of curative doses of LMWH has however not yet been established, regardless of the cause, extent or clinical severity of cerebral infarction. (2) Acute infectious endocarditis (except for some emboligenic cardiac conditions); (3) mild to moderate kidney failure (creatinine clearance over 30 and under 60 ml/min); (4) co-administration with acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses, NSAIDs (systemic use), or Dextran 40 (parenteral use). - See full SmPC. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** (1) Hemorrhagic risk: The recommended dose regimens must be respected (dosages and duration of treatment). Failure to comply with these recommendations can lead to hemorrhage, particularly in high-risk patients (e.g. the elderly, patients with renal failure). Serious hemorrhagic events have been reported in the following situations; elderly subjects, particularly due to age-related renal impairment, kidney failure, weight below 40 kg, treatment lasting longer than the recommended mean duration of 10 days, non-compliance with treatment recommendations (particularly treatment duration and dose adjustment based on body weight in curative treatment), co-administration with drugs increasing the risk of hemorrhage. In all cases, special monitoring is essential in the elderly and/or patients with renal failure, as well as in patients with treatment prolonged beyond 10 days. Assay of anti-Xa activity may in certain cases be useful in detecting drug accumulation (2) Risk of heparin-induced thrombocytopenia (HIT): If a patient treated with low molecular weight heparin (LMWH) (at curative or preventive doses) develops thrombotic complications, such as; exacerbation of the thrombosis being treated, phlebitis, pulmonary embolism, acute ischemia of the lower limbs, or even myocardial infarction or ischemic stroke, heparin-induced thrombocytopenia (HIT) must systematically be suspected and a platelet count performed immediately (3) Use in children: As no relevant data is available, the use of LHWH is not recommended in children (4) Mechanical prosthetic heart valves: Use of enoxaparin in the prevention of thromboembolic complications in patients with mechanical prosthetic heart valves has not specially been studied. Nevertheless, some isolated cases of thrombosis have been reported in patients with mechanical prosthetic heart valves receiving enoxaparin for the prevention of thromboembolic complications (5) Pregnant women: In a clinical study in pregnant women with mechanical prosthetic heart valves who received 100 anti-Xa IU/kg enoxaparin twice daily to reduce the risk of thromboembolic complications, 2 out of 8 women developed thrombosis resulting in blockage of the valve, leading to maternal and fetal death. There have also been isolated post marketing cases of valve thrombosis in pregnant women with mechanical prosthetic heart valves receiving enoxaparin for the prophylaxis of thromboembolic complications. Therefore, the risk of thromboembolic complications in these patients could be higher (6) Medical prophylaxis: If there is an acute episode of infectious or rheumatic disease, prophylactic treatment is only justified if at least one of the following risk factors of venous thromboembolism is also present; age more than 75 years, cancer, history of venous thromboembolism, obesity, hormone treatment, heart failure, chronic respiratory failure. For medical prophylaxis, there is very limited experience available in patients over the age of 80 years with a body weight less than 40 kg. See full SmPC. **DRUG INTERACTIONS:** Certain drugs or therapeutic classes may promote the occurrence of hyperkalemia, e.g. potassium salts, potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs, heparin (low molecular weight or unfractionated), cyclosporin, tacrolimus and trimethoprim. Occurrence

of hyperkalemia may depend on whether the patient has related risk factors. This risk is potentiated when the above-mentioned drugs are co-administered. (I) In subjects less than 65 years of age on curative doses of LMWH, and in elderly subjects (older than 65 years) irrespective of the LMWH dose (1) Inadvisable combinations (a) Acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses (and, by extrapolation, other salicylates): increased risk of bleeding (salicylate-induced platelet function inhibition and gastroduodenal mucosal damage). A non-salicylate antipyretic analgesic should be used (e.g. paracetamol) (b) Nonsteroidal anti-inflammatory drugs (systemic use): increased risk of bleeding (NSAID-induced platelet function inhibition and gastroduodenal mucosal damage). If co-administration cannot be avoided, close clinical monitoring is required (c) Dextran 40 (parenteral use): increased risk of bleeding (inhibition of platelet function by Dextran 40); (2) Combinations requiring precautions for use (a) Oral anticoagulants: potentiation of the anticoagulant effect. When heparin is replaced by an oral anticoagulant, clinical monitoring must be intensified; (3) Combinations to be taken into consideration (a) Platelet aggregation inhibitors (other than acetylsalicylic acid at analgesic, antipyretic and anti-inflammatory doses): abciximab, acetylsalicylic acid at antiaggregant doses in cardiological and neurological indications, beraprost, clopidogrel, eptifibatide, iloprost, ticlopidine, tirofiban: increased risk of bleeding. (II) Patients aged less than 65 years on preventive doses of LMWH the following combinations to be taken into consideration; combined use of drugs affecting various stages of hemostasis potentiates the risk of bleeding. Therefore, regardless of patient age, continued clinical monitoring and, if necessary, laboratory tests must be performed when co-administering LMWHs at prophylactic doses with oral anticoagulants, platelet aggregation inhibitors (abciximab, NSAIDs, acetylsalicylic acid at any dose, clopidogrel, eptifibatide, iloprost, ticlopidine, tirofiban) and thrombolytic agents. - See full SmPC. **PREGNANCY AND LACTATION:** (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:** (1) Hemorrhagic symptoms: These are mainly related to (a) the presence of associated risk factors: organic lesions liable to bleed and certain drug combinations, age, renal failure, low body weight;(b) failure to comply with therapeutic recommendations, particularly treatment duration and dose adjustment based on body weight. Rare cases of spinal hematoma have been reported following administration of low molecular weight heparin during spinal anesthesia, analgesia or epidural anesthesia. These reactions have resulted in varying degrees of neurologic injuries, including long-term or permanent paralysis. Subcutaneous administration can cause hematomas at the injection site. This risk is increased if the recommended injection technique is not respected or if inappropriate injection material is used. Hard nodules, which disappear within a few days, may develop as a result of an inflammatory reaction and do not require treatment discontinuation. (2) Thrombocytopenia has been reported. There are two types (a) Type I, i.e. the most common, is usually moderate (>100 000/mm3), of early onset (before the 5th day), and does not require treatment discontinuation; (b) Type II, i.e. rare, serious immune-allergic thrombocytopenia (HIT). The incidence remains poorly evaluated. (3) Possible asymptomatic and reversible elevation of the platelet count. (4) Rare skin necrosis, observed in most cases at the injection site, has been reported with heparins. These reactions may be preceded by purpura or by infilltrated, painful erythematous plaques. Treatment must be discontinued immediately in these cases. (5) Rare skin or systemic allergic manifestations have occurred, leading to treatment discontinuation in certain cases. (6) The risk of osteoporosis cannot be ruled out if treatment is prolonged, as with unfractionated heparin. (7) Transient elevation of transaminase levels has been reported. (8) A few cases of hyperkalemia have been reported. (9) In very rare cases, vasculitis due to skin hypersensitivity has been reported. (10) Very rarely, hypereosinophilia, has occurred in isolated cases or along with skin reactions, resolving on treatment discontinuation. - see full SmPC. **OVERDOSAGE:** Accidental overdose following subcutaneous administration of massive doses of low molecular weight heparin may result in hemorrhagic complications. The protamine dose required depends on (1) the heparin dose injected (100 anti-heparin units of protamine neutralizes the activity of 100 IU anti-Xa of low molecular weight heparin), if enoxaparin sodium was administered within the last 8 hours, (2) the time since the heparin injection; (a) an infusion of protamine 50 anti-heparin units for enoxaparin sodium 100 IU anti-Xa may be administered if enoxaparin sodium was given more than 8 hours previously, or if a 2nd dose of protamine seems necessary; (b) if the injection of enoxaparin sodium was given more than 12 hours previously, it is not necessary to administer protamine. These recommendations concern patients with normal renal function receiving repeated doses. Nevertheless, the anti-Xa activity cannot be completely neutralized. Furthermore, the neutralization may be transient due to the absorption pharmacokinetics of LMWH, which may require dividing the total calculated dose of protamine into several injections (2-4) given over 24 hrs. In principle, no serious consequences are likely after ingestion of LMWH, even in massive quantities (no cases reported), due to the very low gastric and intestinal absorption of the drug. See full SmPC. **MARKETING AUTHORIZATION HOLDER:** sanofi aventis France 1-13 bd Romain Rolland 75014 Paris, France. Date of Revision of Abbreviated Prescribing Information: March,2017