Prescribing Information: Clexane® (enoxaparin sodium) & Clexane® Forte Solution for Injection in pre-filled syringes

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentations: Clexane® single dose pre-filled syringes containing either: 2,000 IU (20mg) enoxaparin sodium in 0.2ml, 4,000 IU (40mg) enoxaparin sodium in 0.4ml, 6,000 IU (60mg) enoxaparin sodium in 0.6ml, 8,000 IU (80mg) enoxaparin sodium in 0.8ml or 10,000 IU (100mg) enoxaparin sodium in 1ml. Clexane® Forte single dose pre-filled syringes containing either: 12,000 IU (120mg) enoxaparin sodium in 0.8ml or 15,000 IU (150mg) enoxaparin sodium in 1ml.

Indications: 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 (VTE); treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery; extended treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of its recurrence in patients with active cancer; prevention of thrombus formation in extracorporeal circulation during haemodialysis; 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).

Dosage & Administration: Each pre-filled syringe is for single use only. ***Prophylaxis of VTE in Surgical Patients:*** With moderate risk of thromboembolism, recommended dose of enoxaparin sodium is 2,000 IU (20mg) once daily by subcutaneous (SC) injection. Initiation 2hrs before surgery was proven effective and safe in moderate risk surgery. Treatment should be maintained for at least 7-10 days whatever the recovery status (e.g. mobility) and should be continued until the patient no longer has significantly reduced mobility. In patients at high risk of thromboembolism, the recommended dose of enoxaparin sodium is 4,000 IU (40mg) once daily by SC injection preferably started 12hrs before surgery. Need for earlier than 12hrs enoxaparin sodium preoperative prophylactic initiation (e.g. high-risk patient waiting for a deferred orthopaedic surgery), the last injection should be administered no later than 12hrs prior to surgery and resumed 12hrs after surgery. For patients undergoing major orthopaedic surgery an extended thromboprophylaxis up to 5 weeks is recommended. For patients with high risk of VTE undergoing abdominal or pelvic surgery for cancer, extended thromboprophylaxis up to 4 weeks is recommended. ***Prophylaxis of VTE in Medical Patients:*** Recommended dose of enoxaparin sodium is 4,000 IU (40mg) once daily by SC injection. Treatment with enoxaparin sodium is prescribed for at least 6-14 days. Benefit is not established for treatment longer than 14 days. ***Treatment of DVT/PE:*** 150 IU/kg (1.5mg/kg) administered SC once daily should be used in uncomplicated patients with low risk of VTE recurrence. 100 IU/kg (1mg/kg) twice daily should be used in all other patients such as those with obesity, symptomatic PE, cancer, recurrent VTE or proximal (vena iliaca) thrombosis. The regimen should be selected based on individual assessment including evaluation of the thromboembolic risk and risk of bleeding. Enoxaparin sodium treatment is prescribed for an average period of 10 days. Oral anticoagulant therapy should be initiated when appropriate. ***Extended treatment of DVT and PE and prevention of its recurrence in patients with active cancer****:* physicians should carefully assess the individual thromboembolic and bleeding risks of the patient. The recommended dose is 100 IU/kg (1 mg/kg) twice daily by SC injection for 5 to 10 days followed by a 150 IU/kg (1.5 mg/kg) once daily SC injection up to 6 months. The benefit of continuous anticoagulant therapy should be reassessed after 6 months of treatment. ***Treatment of Acute Coronary Syndromes:*** For treatment of unstable angina and NSTEMI, the recommended dose of enoxaparin sodium is 100 IU/kg (1mg/kg) every 12hrs by SC injection administered in combination with antiplatelet therapy. Treatment should be for a minimum of 2 days and until clinical stabilization (usual duration 2 to 8 days). Acetylsalicylic acid recommended for all patients without contraindications at an initial oral loading dose of 150–300mg (in acetylsalicylic acid-naive patients) and a maintenance dose of 75–325mg/day long-term. For treatment of acute STEMI, recommended dose of enoxaparin sodium is a single intravenous (IV) bolus of 3,000 IU (30mg) plus a 100 IU/kg (1mg/kg) SC dose followed by 100 IU/kg (1mg/kg) administered SC every 12hrs (maximum 10,000 IU (100mg) for each of the first 2 SC doses). Appropriate antiplatelet therapy such as oral acetylsalicylic acid (75mg to 325mg once daily) should be administered concomitantly unless contraindicated. Recommended duration of treatment is 8 days or until hospital discharge. 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. For patients managed with PCI, if the last dose of enoxaparin sodium SC was given less than 8hrs before balloon inflation, no additional dosing needed. If the last SC administration was given more than 8hrs before balloon inflation, an IV bolus of 30 IU/kg (0.3mg/kg) enoxaparin sodium should be administered. ***During haemodialysis:*** 100 IU/kg (1mg/kg) enoxaparin sodium introduced into arterial line of the circuit at beginning of dialysis. This dose is usually sufficient for a 4-hour session. If fibrin rings are found, e.g. after a longer session, a further 50 to 100 IU/kg (0.5 to 1mg/kg) may be given. In patients with high risk of haemorrhage reduce the dose to 50 IU/kg (0.5mg/kg) (double vascular access) or 75 IU/kg (0.75mg/kg) (single vascular access).

Special Populations: ***Elderly ≥75 years of age:*** For treatment of acute STEMI, an initial IV bolus must not be used. Initiate dosing with 75 IU/kg (0.75mg/kg) SC every 12hrs (maximum 7,500 IU (75mg) for each of the first 2 SC doses only, followed by 75 IU/kg (0.75mg/kg) SC dosing for the remaining doses). ***Paediatric:*** Safety and efficacy not established. ***Renal impairment:*** Dosage adjustment required for patients with severe renal impairment (creatinine clearance 15-30 mL/min). Not recommended for patients with end stage renal disease (creatinine clearance <15 mL/min. ***Hepatic Impairment***: Limited data in this population therefore caution should be used.

Contraindications: Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including low molecular weight heparins (LMWH) or any of the excipients. Recent (<100 days) history of immune mediated heparin-induced thrombocytopenia (HIT) 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/ suspected oesophageal varices, arteriovenous malformations, vascular aneurysms/ major intraspinal/ intracerebral vascular abnormalities. Spinal/ epidural/ loco-regional anaesthesia when enoxaparin sodium is used for treatment in the previous 24hrs.

Warnings and Precautions: Do not use interchangeably (unit for unit) with other LMWHs. ***History of HIT (>100 days) without circulating antibodies:*** Use with extreme caution in these patients and only after careful benefit-risk assessment and non-heparin alternative treatments are considered. ***Monitoring of platelet counts:*** In patients with cancer with a platelet count below 80 g/L, anticoagulation treatment can only be considered on a case-by-case basis and careful monitoring is recommended. There is a risk of antibody-mediated HIT, which is higher in postoperative patients and mainly after cardiac surgery and in patients with cancer. It is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin sodium and then regularly thereafter during the treatment; or if clinical symptoms suggestive of HIT are experienced. Patients must be aware of the symptoms and told to inform their primary care physician if experienced. If a confirmed significant decrease of the

platelet count is observed (30-50% of the initial value), enoxaparin sodium treatment must be immediately discontinued, and the patient switched to another non-heparin anticoagulant alternative treatment. ***Haemorrhage:*** Use with caution in conditions with increased potential for bleeding (e.g. 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:*** Increases in activated partial thromboplastin time (aPTT) and activated clotting time (ACT) may occur at higher doses but not linearly correlated with increasing enoxaparin sodium antithrombotic activity***. Spinal/epidural anaesthesia or lumbar puncture:*** must not be performed within 24hrs of administration of therapeutic doses 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. ***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 this condition. ***Mechanical prosthetic heart valves:*** Enoxaparin sodium has not been adequately studied for thromboprophylaxis in patients (including in pregnancy) with mechanical prosthetic heart valves. ***Elderly patients (especially >80 years old):*** may be at increased risk of bleeding complications at therapeutic doses. ***Hepatic impairment:*** Enoxaparin sodium should be used with caution in these patients. In patients with liver cirrhosis dose adjustment based on monitoring of anti-Xa levels is unreliable and not recommended. ***Renal impairment:*** There is an increased risk of bleeding for these patients therefore 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. In patients with severe renal impairment (creatinine clearance 15-30 mL/min) a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. ***Low body weight patients:*** are at increased risk of bleeding at prophylactic and treatment dose ranges. ***Obese patients:*** are at higher risk for thromboembolism however there is no consensus for dose adjustment; these patients should be observed carefully. ***Hyperkalaemia:*** Heparins can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, taking medicinal products known to increase potassium; plasma potassium should be monitored regularly especially in patients at risk. ***Traceability:*** 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. ***Sodium:*** For patients receiving doses >210mg/day, this medicine contains >24mg sodium, equivalent to 1.2% of the recommended maximum daily intake of sodium for an adult. ***Acute generalized exanthematous pustulosis:*** Acute generalized exanthematous pustulosis (AGEP) has been reported with frequency not known in association with enoxaparin treatment. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, enoxaparin should be withdrawn immediately and an alternative treatment considered (as appropriate). **Pregnancy and Lactation:** 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. If an epidural anaesthesia is planned, it is recommended to withdraw treatment before. Enoxaparin sodium can be used during breastfeeding. **Interactions*: Not Recommended:*** Systemic salicylates, acetylsalicylic acid at anti-inflammatory doses, and NSAIDs including ketorolac. Other thrombolytics and anticoagulants. ***Caution:*** Platelet aggregation inhibitors including acetylsalicylic acid used at anti-aggregant 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.

Adverse Reactions: ***Very Common:*** Hepatic enzyme increases (mainly transaminases > 3 times the upper limit of normality). ***Common:*** Haemorrhage, haemorrhagic anaemia, thrombocytopenia, thrombocytosis, allergic reaction, headache, urticaria, pruritus, erythema, injection site haematoma / pain / other reaction (such as oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction). ***Uncommon:*** Hepatocellular liver injury, bullous dermatitis, local irritation, skin necrosis at injection site. ***Rare:*** Eosinophilia, cases of immuno-allergic thrombocytopenia with thrombosis (in some cases thrombosis was complicated by organ infarction or limb ischaemia), anaphylactic/anaphylactoid reactions including shock, spinal/neuraxial haematoma resulting in varying degrees of neurologic injuries including long-term or permanent paralysis, cholestatic liver injury, alopecia, cutaneous vasculitis, skin necrosis, injection site nodules, osteoporosis following therapy > 3 months, hyperkalaemia. ***Not known:*** Acute generalized exanthematous pustulosis. Please refer to the SPCs for full details. **Legal Category:** POM. **Marketing Authorisation (MA) Numbers:** Clexane 2,000IU: PA540/97/4; Clexane 4,000IU: PA540/97/5; Clexane 6,000 IU: PA540/97/6; Clexane 8,000 IU: PA540/97/7; Clexane 10,000 IU: PA540/97/1; Clexane Forte 12,000 IU: PA540/97/8; Clexane Forte 15,000 IU: PA540/97/2 **MA Holder and further information is available on request from:** Sanofi Ireland Ltd., 18 Riverwalk, Citywest Business Campus, Dublin 24 or contact IEmedinfo@sanofi.com Tel: 01 403 5600. **Date of Preparation: February 2022. Document no. MAT-IE-MAT-IE-2200013v1.0)**

Adverse events should be reported. Reporting forms and information can be found at: www.hpra.ie;
E-mail: medsafety@hpra.ie
Adverse events can also be reported to Sanofi Ireland Ltd. Tel: 01 403 5600.

Alternatively, send via Email to IEPharmacovigilance@sanofi.com