Direct Healthcare Professional Communication, Clexane (enoxaparin sodium): Updates to strength expression, dose regimens in DVT/PE, use in patients with severe renal impairment

Information to general practitioners, Trust medical directors, orthopaedic, general, vascular and gynaecological surgeons, general, acute and respiratory physicians, cardiologists, nephrologists, haematologists, pharmacists and nurses.

Dear Healthcare Professional,

Sanofi, in agreement with the European Medicines agency and the Medicines and Healthcare products Regulatory Agency (MHRA), would like to inform you that following completion of a Europe-wide review, the product information for Clexane (enoxaparin sodium) has been harmonised in all European Union (EU) countries. Strength expression, dose regimens in deep vein thrombosis (DVT)/pulmonary embolism (PE) and use in patients with severe renal impairment are updated as follows:

Summary

- **Enoxaparin strength previously expressed in milligrams (mg) will now be expressed both in international units (IU) of anti-Xa activity and in milligrams (mg): One mg of enoxaparin sodium is equivalent to 100 IU anti-Xa activity.**

  For example for the pre-filled syringes of 0.4 ml, the strength will appear as: Clexane Syringes 4,000 IU (40 mg)/0.4 ml solution for injection.

- **The dosage in treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) has been clarified as follows:**

  Enoxaparin sodium can be administered subcutaneously:

  - **either as a once daily injection of 150 IU/kg (1.5 mg/kg):** used in uncomplicated patients with low risk of venous thromboembolism (VTE) recurrence.
  - **or as twice daily injections of 100 IU/kg (1 mg/kg):** used in all other patients such as those with obesity, with symptomatic PE, cancer, recurrent VTE or proximal (iliac vein) thrombosis.

  The regimen should be selected by the physician based on an individual assessment including evaluation of the thromboembolic risk and the bleeding risk.

- **Use in patients with end stage kidney disease (creatinine clearance <15 ml/min) is not recommended outside the prevention of thrombus formation in haemodialysis patients.**

<u>Background on the safety concern</u>

Important discrepancies existed between EU member states in the way enoxaparin strength was expressed in the product denomination and throughout the product information, the approved dosage regimen in DVT/PE and use in severe renal impairment.

Expressing strength both in IU and mg provides healthcare professionals clarity about enoxaparin doses regardless of which style they are familiar with, and will avoid medication error leading to risk of thrombosis or major bleeding.

A once daily 150 IU/kg (1.5 mg/kg) or a twice daily 100 IU/kg (1 mg/kg) regimen or both regimens were approved in the member states for the treatment of DVT/PE. Whilst keeping mention of the two dose regimens, these have been harmonised by strengthening recommendations about the populations in which the possible regimens should be used.

A contraindication in patients with severe renal impairment (creatinine clearance < 30 ml/min) that existed in some EU member states was removed from the product information (as needed), however, use in patients with end stage kidney disease (creatinine clearance <15 ml/min) is not recommended outside the prevention of thrombus formation in haemodialysis patients due to lack of data in this population.

For patients with severe renal impairment (creatinine clearance [15-30] ml/min) the following dose adjustment is recommended:

Indication	**Dosing regimen**
Prophylaxis of venous thromboembolic disease	2,000 IU (20 mg) SC once daily
Treatment of DVT and PE	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of unstable angina and Non ST-segment elevation myocardial infarction	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of acute ST-segment elevation myocardial infarction (patients under 75)	1 x 3,000 IU (30 mg) IV bolus plus 100 IU/kg (1 mg/kg) body weight SC and then 100 IU/kg (1 mg/kg) body weight SC every 24 hours
Treatment of acute ST-segment elevation myocardial infarction (patients over 75)	No IV initial bolus, 100 IU/kg (1 mg/kg) body weight SC and then 100 IU/kg (1 mg/kg) body weight SC every 24 hours

Further Information

Enoxaparin is a low molecular weight heparin.

On 15 December 2016, the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) adopted the European labelling harmonisation for efficacy and safety information of Clexane.

This letter will also be available on the eMC website (www.medicines.org.uk), where it will be found in association with the product information for Clexane (enoxaparin sodium).

Call for reporting

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Adverse events arising from the use of medicines manufactured by Sanofi may also be reported to the **Sanofi UK Pharmacovigilance** department at: Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS; Tel: 0800 0902314; Fax: 0800 4716122; Email: uk-drugsafety@sanofi.com

Company contact point

Should you have any question or require additional information, please contact **Medical Information** at Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS, UK; Tel: 0845 372 7101;
Email: uk-medicalinformation@sanofi.com.

Yours faithfully,

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