

Annex II
Scientific conclusions

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Enoxaparin sodium is a low molecular weight heparin marketed under the trade names Lovenox and associated names. This anticoagulant is used in the treatment and prophylaxis of thromboembolic disorders. It is given as an injection subcutaneously or intravenously. Lovenox and associated names is authorised in all EU member states (MSs) as well as in Iceland and Norway.

The principal pharmacological properties of enoxaparin include antifactor Xa and antifactor IIa (antithrombin) activity, which are dependent on its binding affinity for antithrombin. Lovenox and associated names solution for injection is currently approved in more than 140 countries worldwide including all the European Union (EU) member states as well as Norway and Iceland. The first marketing authorisation (MA) was granted in France on 03 April 1987.

The product is currently registered in the EU under concentrations of 100 mg/mL (equivalent to 10 000 IU anti Xa/mL) in prefilled syringes, multi-dose vials, ampoules, and 150 mg/mL (equivalent to 15 000 IU anti Xa/mL) in prefilled syringes. Vials of 100 mg/10 mL and a pen of 10 x 40 mg (equivalent to 10 x 4 000 IU anti Xa) are also authorised.

Due to the divergent national decisions taken by Member States (MSs) concerning the authorisation of the above-mentioned product and its associated names, France notified the CHMP/European Medicines Agency of a referral under Article 30 of Directive 2001/83/EC for the above-mentioned product, in order to resolve divergences amongst the nationally authorised product information (PI) and thus to harmonise its divergent PIs across the EU.

Overall summary of the scientific evaluation by the CHMP

The Product Information was split as follows according to the indications the individual products are approved for:

- The Summary of Product Characteristics (SmPC) and Package Leaflet (PL) covering vials, ampoules and prefilled syringes covers all approved indications,
- The presentation 10,000 IU (100 mg)/10 mL solution for injection is used only for extracorporeal dialysis, and hence only this indication is covered in section 4.1,
- The pen presentation (10 x 4,000 IU (10x 40 mg)) contains all approved indications except use in extracorporeal dialysis.

Section 1 – Name of the medicinal product and Section 2 – Qualitative and quantitative composition

The strength of the product is expressed differently in the different MSs, either in mg or in activity IU anti-factor Xa.

On one hand, an expression and dosing in mg is consistent with the approvals in the majority of the EU and allows both identification and distinction between different presentations whilst favouring ease of prescribing, dosing, dispensing and administration. On the other hand, other low molecular weight heparins (LMWHs) in most European MSs are mainly expressed in IU of activity anti Xa and not in mg, which is in line with the European Pharmacopoeia (Version 8.1, 2014), which expresses the strength of heparins, including LWMH in IU of activity anti Xa. As harmonisation of expression of strength to one of the options would have led to changes to the established practice in several countries, and as this may increase the risk of medication errors leading to higher risk of thrombosis or major bleeding, the wording has been amended to express

the strength in both units (in IU anti-Xa/mL and its equivalence in mg/ml) on the outer-carton and immediate packaging (syringe) and in sections 1, 2 and 4.2.

Section 4.1 – Therapeutic Indications

The section was harmonised to address variations in the exact wording in prophylaxis and treatment indications. Furthermore, the indications were not the same depending on the strength of the product, which was addressed as part of the referral.

Prophylaxis of venous thromboembolism (VTE) in surgical patients

For prophylaxis of venous thromboembolism (VTE) in surgical patients, the CHMP considered that it would be relevant to label the indication on the patient's level of thrombotic risk in line with the American College of Clinical Pharmacy (ACCP) Guidelines. The harmonised indication therefore states 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 VTE in medical patients

The terminology used for the indication prophylaxis of venous thromboembolism in medical patients varied across Member States. The CHMP referred also for this indication to the existing ACCP guidelines, and further preferred a wording more in line with the current recommendations for thromboprophylaxis in acutely ill medical patients in the literature. The wording for the indication in this population therefore includes now 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 venous thromboembolism

For treatment of deep venous thromboembolism, the exact wording varied across Member States, and the CHMP considered harmonising the indication to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) excluding PE likely to require thrombolytic therapy or surgery. The harmonised indication is based on treatment guidelines (European Society of Cardiology (ESC), and ACCP), as well as clinical study and literature data presented by the MAH.

Treatment of unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI)

The treatment of UA and NSTEMI was not authorised in all Member States prior to the finalisation of this referral.

In view of this indication, the CHMP noted the consensus document of the Joint ESC/American College of Cardiology Committee for the redefinition of myocardial infarction (MI), which led to the revision of the definition of acute coronary syndromes (ACS) to UA and NSTEMI. The CHMP agreed to use this definition in the enoxaparin labelling, and the indication was harmonised to include treatment of unstable angina and NSTEMI administered concurrently with oral acetylsalicylic acid.

Treatment of acute ST-segment elevation myocardial infarction (STEMI)

For treatment of acute ST-segment elevation myocardial infarction, the CHMP noted that the pivotal study (ExTRACT-TIMI 25) was carried out in STEMI patients fulfilling the following criteria:

- Medically managed patients (not undergoing primarily invasive procedure such as percutaneous coronary intervention (PCI) or coronary bypass artery surgery (CABG));

Patients in whom PCIs could be performed at any time for failed fibrinolysis or urgently in case of recurrent myocardial ischemia/infarction, but had to be deferred in other situations at least for 48 hours.

The CHMP adopted a wording, which is in agreement with the clinical data and treatment guidelines (grade IIbB in ESC guidelines 2012, American Heart Association (AHA) guideline 2011).

Prevention of extracorporeal thrombus during haemodialysis

In view of prevention of extracorporeal thrombus during haemodialysis, all Member States had this indication in the PI, except the Netherlands who did not find the data using the dosing scheme proposed at the time of initial Marketing authorisation sufficient. However, no further important differences exist for the haemodialysis indication in the national SmPCs approved in the EU MSs. The CHMP considered keeping the indication in line with the most common wording accepted in the countries.

Section 4.2 – Posology and method of administration

In general, the sub-sections on posology and method of administration were aligned with the harmonised indications for enoxaparin.

Prophylaxis of venous thromboembolic disease

For this indication in moderate and high risk surgical patients the CHMP considered that the SmPC should reflect that individual thromboembolic risk for patients can be estimated using a validated risk stratification model. Dosing in prophylaxis of venous thromboembolism in medical patients was harmonised to be aligned with ACCP guidelines.

Treatment of DVT and pulmonary embolism PE

For treatment of DVT and PE the CHMP considered, based on the data provided and available treatment guidelines, that the harmonised wording should include a once daily injection of 150 IU/kg (1.5 mg/kg) or a twice daily injections of 100 IU/kg (1 mg/kg) in DVT and PE patients. The CHMP also considered that 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.

Prevention of thrombus formation during haemodialysis

In terms of posology for this indication most of the countries stated a dose of enoxaparin 1mg/kg and a few countries stated a lower dose for this indication. Doses studied in the clinical studies vary from 0.5 mg/kg to 1.25 mg/kg. The SmPC was aligned to state the recommended dose as accepted in most countries of 1mg/kg, which is in line with the clinical data and with the recommendations from treatment guidelines.

Unstable angina and NSTEMI indications

No difference exists between countries in terms of enoxaparin dosage regimen (1 mg/kg every 12 hours by subcutaneous injection) in these indications. However, the CHMP considered that acetylsalicylic acid (ASA) should be recommended at dose from 75 mg to 325 mg in the SmPC to be in line with clinical data and clinical practice.

Treatment of acute STEMI

Some disharmonies existed further in terms of the timing of enoxaparin administration in this indication, which were aligned as part of the procedure. The CHMP noted that in the current ESC guideline, ASA is recommended for all patients without contraindications at an initial oral loading

dosed of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg/day long-term regardless of the treatment strategy. For STEMI, the higher dose on the first day as used in the study EXTRACT-TIMI 25 should be mentioned.

Other populations

Due to divergent information across Member States, updates were also made in further sub-sections including paediatric population, elderly, hepatic and renal impairment in line with the agreed indications and based on available data in these populations. Further sub-sections were added to provide information on switch between enoxaparin sodium and oral anticoagulants as well as recommendations for administration in spinal/epidural anaesthesia or lumbar puncture.

Section 4.3 – Contraindications

This section was harmonised to reflect in a uniform way the following contraindications, of which not all were included across the EU, or different terminologies were used:

- Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including other low molecular weight heparins (LMWH) or to any of the excipients;
- 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;
- History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies (see also section 4.4);
- spinal or epidural anaesthesia or loco-regional anaesthesia when enoxaparin sodium is used for treatment in the previous 24 hours (with a reference to section 4.4);
- use of multiple dose vials containing benzyl alcohol in newborns or premature neonates due to risk of gasping syndrome in this population.

Some Member States had a contra-indication for severe renal impairment (clearance < 30 mL/min) in the therapeutic indications, which has been removed as part of the referral based on available data supporting use in this population. A previously existing contraindication for use in patients with end stage renal disease (creatinine clearance <15 mL/min) was also removed due to lack of safety data in this population justifying a contraindication, however use in this population is not recommended, as outlined below.

Section 4.4 – Special warnings and precautions for use

Revisions were made to this section to add the risk of acute infectious endocarditis. A consistent wording has been approved on platelet count monitoring to take into account current international guidelines, in order to avoid unnecessary monitoring in patients at low risk of HIT. Other changes were made to complement the information already present in other parts of the product information:

- reduction of dosage in patients above 75 years old treated by enoxaparin for ST-segment elevation myocardial infarction (STEMI);
- increase in the risk of hepatic impairment;
- careful biological monitoring by anti-Xa activity measurement in renally impaired patients;

- use of enoxaparin is not recommended for patients with end stage renal disease due to lack of data in this population outside the prevention of thrombus formation in dialysis patients;
- 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;
- increased potential bleeding;
- to be used with extreme caution in patients with a history (>100 days) of heparin-induced thrombocytopenia without circulating antibodies;
- not to use perform spinal/epidural anaesthesia or lumbar puncture during treatment with enoxaparin;
- discontinue treatment in case of skin necrosis and cutaneous vasculitis.

Finally a wording was added to foster traceability of biological medicinal products. Other sections such as “hyperkalaemia” were included as these were not uniformly worded across Member States.

Other sections of the SmPC

Sections 4.5 to 6 have been harmonised based on relevant available information or amended according to the latest QRD template. These changes were mostly technical in nature and therefore not discussed in detail here.

Labelling

Changes introduced in the SmPC were consistently reflected in the labelling where relevant, however some sections were left to be completed nationally.

Package Leaflet (PL)

The PL has been harmonised taking into account all revisions of the SmPC that are relevant to the PL.

Direct Healthcare Provider Communication (DHPC)

Taking into account the risk of medication errors and the clarification as regards indications and contraindications, the CHMP agreed the following key messages to be used in a direct healthcare professional communication (DHPC) to general practitioners, orthopaedics, internists, cardiologists, haematologists, surgeons, pharmacists, nurses (or other as per national health care system):

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

For example, for pre-filled syringes of 0.4 ml, the strength will appear as:
<Local tradename> 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 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 (vena iliaca) thrombosis.

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

- 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, however, use in patients with end stage kidney disease (creatinine clearance < 15 ml/min) is not recommended outside the prevention of thrombus formation in dialysis patients.

Grounds for the CHMP opinion

Whereas

- the scope of the referral was the harmonisation of the product information,
- the product information proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,
- the Committee considered the referral under Article 30 of Directive 2001/83/EC,
- the Committee considered the divergences identified in the notification for Lovenox and associated names, as well as the remaining sections of the product information,
- the Committee reviewed the totality of the data submitted by the MAH in support of the proposed harmonisation of the product information,
- the Committee agreed on a harmonised product information for Lovenox and associated names,

the CHMP recommended the variation to the terms of the marketing authorisations for which the product information is set out in Annex III for Lovenox and associated names (see Annex I).

The CHMP as a consequence, concluded that the benefit-risk balance of Lovenox and associated names remains favourable, subject to the agreed changes to the product information and the condition to the marketing authorisation.