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Committee for Medicinal Products for Human Use

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Lovenox and associated names

INN: enoxaparin

Procedure number: EMEA/H/A-30/1429

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information

Due to the divergent national decisions taken by Member States (MSs) concerning the authorisation of the above-mentioned product, France notified the Committee for Medicinal Products for Human Use (CHMP)/European Medicines Agency on 12 November 2015 of a referral under Article 30 of Directive 2001/83/EC for Lovenox and associated names, in order to resolve divergences amongst the nationally authorised product information and thus harmonise its divergent product information across the EU.

2. Scientific discussion

2.1. Introduction

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, intravenously or in the arterial line of a dialysis circuit. Lovenox and associated names is authorised in all European Union (EU) member states 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 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 International Unit (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:

- Pre-filled syringes: 20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml, 100 mg/1.0 ml), 90 mg/0.6 ml, 120 mg/0.8 ml, 150 mg/1.0 ml,
- Multi-dose vials: 300 mg/3 ml, 500 mg/5 ml, 1000 mg/10 ml,
- Ampoules: 20 mg/0.2 ml, 40 mg/0.4 ml, 100mg/1.0 ml,

Of note, Marketing Authorisations for cartridge presentations (20 mg/0.2 ml, 40 mg/0.4 ml) have been withdrawn upon request by the Marketing Authorisation Holder (MAH) since the initiation of the referral.

In Austria presentations of vials of 100 mg/10 ml and pen 10 x 40 mg are also authorised.

Due to the divergent national decisions taken by Member States 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 PI across the EU.

2.2. Critical Evaluation

2.2.1. Product information

The PI 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 in extracorporeal circulation during haemodialysis, 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 in extracorporeal circulation during haemodialysis.

2.2.1.1. Summary of Product Characteristics

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 member states, either in mg or in activity in terms of IU anti-factor Xa. In 12 countries, enoxaparin sodium strength is expressed in terms of IU, while in 17 countries enoxaparin is expressed in mg. In Malta both expressions are used.

Table 1: Strength expression in the name of the medicinal product

	EU countries
UI AntiXa	CY, HR, CZ, EE, FR, EL, IT, LV, LT, MT, RO ,SK ,SI
mg	AT, BE/LU, BG, DK, FI, DE, HU, IS, IE, MT, NL, NO, PL, PT, ES, SE, UK

Whilst IU is based on the European Pharmacopoeia usage to express the anti-Xa activity potency for Low Molecular Weight Heparin (LMWH), the expression in mg reflects the quantity in active substance.

These differences are based on the following considerations:

- As per the European Medicines Agency QRD recommendation on the expression of strength in the name of the medicinal products, the purpose of the strength in the name of a product is to give the most relevant information regarding the content of the product in view of its use, easy identification and distinction from other presentations, and prescription by the physician, also taking into account other aspects of the medication management process.
- The pharmaceutics of enoxaparin are consistent, leading to a product with predictable anti-Xa and anti-IIa activity from batch to batch. This biological activity is specific to each LMWH and the dosing applicable for enoxaparin is clearly not the same for other LMWHs.
- Considering that 1 mg of enoxaparin exhibits 100 IU anti-Xa, this allows an easy conversion and representation of the anti-Xa activity for the prescriber, and referring to mg instead of biological activity units has been commonly used throughout clinical trials.

The European guideline on SmPCs recommends that “The quantity of biological medicinal products should be expressed in terms of mass units, units of biological activity, or International Units as appropriate for the particular product, and reflecting European Pharmacopoeia usage where relevant.”

The CHMP noted that an expression and dosing in mg is consistent with the approvals in the majority of the EU countries, as well as in numerous other countries worldwide including the USA, Canada, Australia; it allows both identification and distinction between different presentations whilst favouring ease of prescribing, dosing, dispensing and administration. However, other LMWHs in most European MS 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 such, even if the biological activity is specific to each LMWH, the CHMP considered

that using the same units for all heparins (Heparin unfractionated (UFH) and LMWH) would allow standardisation of treatment.

Therefore, although to be in line with the European Guideline on SmPC and the European Pharmacopoeia, expression in terms of activity anti-Xa and not in mg appears preferable, the CHMP was of the opinion that modification of the expression of strength in several countries may increase the risk of medication errors, which may lead to higher risk of thrombosis or major bleeding. The CHMP therefore agreed to mention 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 across the SmPC and PL.

In addition to routine risk minimisation measures, the CHMP agreed key messages to be used in a direct healthcare professional communication (DHPC) to general practitioners, orthopaedics, internists, cardiologists, haematologists, surgeons, pharmacists, and nurses (or other as per national health care system), in addition to the clarification as regards to indications and contraindications (see also section 3 Recommendation).

Section 4.1 – Therapeutic Indications

Overall, the general principles of prophylactic and therapeutic indications of enoxaparin are reflected in the PIs across the EU, however the section was harmonised to address variations in the exact wording in these types of indication, which were different between Member States

The indications were also not the same depending on the strength of the product, the terms “treatment of unstable angina and non-ST segment elevation myocardial infarction (NSTEMI)” were not used consistently in all Member States, and the indications “prophylaxis of VTE in medical patients” and “use in extra corporeal circulation during haemodialysis” were not authorised in some EU countries.

Prophylaxis indications:

Prophylaxis of venous thromboembolism (VTE) in surgical patients

The most frequent disharmonies in the indication section of the national SmPCs related to the prophylaxis of VTE in surgical patients and are limited to differences of wording; some country labels are based on the levels of risk/severity (moderate, high), whereas others specifically cite the type of surgery considered to be at risk.

The indication as labelled by the MAH was mainly based on the patient’s level of risk but also includes the type of surgery.

The 2012 American College of Chest Physicians (ACCP) guidelines recommend the following:

For patients undergoing orthopaedic surgery

- LMWH for a minimum of 10-14 days: Grade 1B
- Starting either 12 h or more preoperatively or 12 h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively: Grade 1B.
- For major orthopaedic surgery, extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days: Grade 2B.

For patients undergoing non orthopaedic surgery

- For patients at moderate risk for venous thromboembolism who are not at high risk for perioperative bleeding, LMWH: Grade 2B.

- Patients at high risk for venous thromboembolism, who are not at high risk for perioperative bleeding, LMWH: Grade 1B.

The CHMP considered that it would be relevant to state the indication based on the patient's level of thrombotic risk in line with these Guidelines.

However, the CHMP considered that mentioning of "peri- or postoperative" settings belong rather to the posology than the indication and should be removed. 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 venous thromboembolism (VTE) in medical patients

There are few differences in the various country labels regarding the indication prophylaxis of VTE in medical patients. While e.g. the term "bedridden" appears in many countries as a key criteria, some countries have more open definition such as "whose position can be defined at risk" or "temporary immobilised".

The ACCP guidelines recommend: For acutely ill hospitalised medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with LMWH, low-dose unfractionated heparin (LDUH) twice a day (BID), LDUH three times a day (TID), or fondaparinux: Grade 1B.

The International Consensus Statement also identified medical patients with heart failure, respiratory disease (…) as being at high risk of thrombosis and requiring thromboprophylaxis (High level).

The revised wording is based on the inclusion criteria and the results of the MEDENOX study (Samama, 1999), and in agreement with the guidelines on medical patients and in line with the current recommendations for thromboprophylaxis in acutely ill medical patients (Kahn, 2012).

The harmonised wording for the indication in this population therefore includes "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 indications

Treatment of deep venous thromboembolism (DVT)

With regards to the deep vein thrombosis (DVT) treatment therapeutic indication, in most MSs enoxaparin sodium is indicated in patients with DVT with or without Pulmonary embolism (PE), while in some countries it is indicated in patients with DVT or PE or both (meaning it may be prescribed in patients with PE alone).

In addition, in some countries there is a mention that some patients should not be treated with enoxaparin sodium, such as for example patients "with signs of clinical seriousness excluding pulmonary embolism likely to require treatment with a thrombolytic agent or surgery" or should only be treated with enoxaparin sodium "when there is no indication for thrombolytic treatment or surgery".

In most enoxaparin trials, PE was not the main inclusion criterion, as included patients had to have a DVT accompanied or not by a PE. The efficacy and safety of enoxaparin in this population was confirmed in a meta-analysis reported above, showing consistent results in patients with DVT with or without PE.

Some trials were conducted using PE as the main inclusion criteria and suggested that enoxaparin can be used effectively and safely for the treatment of PE, but given the small size of the population in these studies, it is proposed that patients with PE only should not be part of the indication.

In view of high risk PE patients, defined as patients requiring thrombolytic therapy or surgery, the CHMP considered that the provided studies were mainly double blinded and randomised. One study (Decousus et al. 1998) specifically enrolled patient with DVT with or without PE and showed that enoxaparin at 100 IU/kg BID was as effective and safe as UFH for the treatment of DVT and PE.

The following guidelines recommend using enoxaparin for the treatment of acute pulmonary embolism at intermediate or low risk with a high level of evidence:

European Society of Cardiology (ESC) guidelines on the diagnosis and management of acute pulmonary embolism: "PE with shock or hypotension (high risk): anticoagulation with UFH (grade IC), PE without shock or hypotension (intermediate or low risk): LMWH or fondaparinux (grade IA)".

ACCP guidelines, 2012: "For acute DVT or PE, initial parenteral anticoagulant therapy (Grade 1B) with LMWH or fondaparinux rather than intravenously (IV) (Grade 2C) or subcutaneously (SC) (Grade 2B) UFH, or anticoagulation with rivaroxaban."

During the procedure the MAH summarised the evidence with regards to treatment of PE, and the CHMP noted that the original program for enoxaparin investigated patients with DVT with or without PE (see table 2 below)

Table 2: Overview of recurrent event rates observed in enoxaparin studies in DVT and PE populations

	Enoxaparin	control	Control treatment
A. Initial treatment of PE			
Pérez de Llano et al.	3/29 (10.7%)	2/21 (9.5%)	UFH
Alonso Martinez et al.	8/65 (13%)	17/38 (44%)	UFH
Findik et al.	0/29	1/30 (3.3%)	UFH
B. Extended treatment with enoxaparin			
Bechmann et al.	3/40 (7.5%)	0/20	UFH/warfarin
Kucher et al.	1/20 (5.0%)	1/20 (5.0%)	enoxaparin/warfarin
C. Enoxaparin used as gold standard			
Büller et al. 2012	43/1603 (2.7%)	34/1599 (2.1%)	Enoxaparin/idrabiotaparinux
Agnelli et al.	23/886 (2.6%)	21/900 (2.3%)	Apixaban
EINSTEIN–PE investigators	44/2413 (1.8%)	50/2420 (2.1%)	Rivaroxaban 4832

The CHMP considered that trials (under A in the above table) comparing enoxaparin to UFH must be seen as pilots and lack power. Still, they can be considered proof of concept.

Trials for extended treatment (under B) do not investigate enoxaparin as initial treatment for PE.

In 3 large new anticoagulant trials (C), enoxaparin was used in the control arm. This may come as a surprise given the limited evidence for use of enoxaparin in PE. It may reflect the conviction of the investigators that suitability for treatment of PE is a class-effect of LMWHs, and/or that evidence for DVT can be extrapolated to PE without hesitation.

Despite the paucity of evidence specifically for PE, and taking into account the original program (DVT with or without PE), the similarities between the various LMWHs (class-effect) and the overlap between the DVT and PE conditions, the proposed indication was considered acceptable.

Overall, the CHMP agreed for not restricting the PE indication to patients with concomitant DVT, and to harmonise the indication to include "treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) excluding PE likely to require thrombolytic therapy or surgery."

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

For this setting, all countries except Germany used the indication as stated in the enoxaparin studies included in the regulatory dossier i.e., "unstable angina and non Q wave myocardial infarction". The German PI is using the current guidelines definition i.e., "unstable angina and NSTEMI".

Enoxaparin in UA and non Q wave myocardial infraction (MI) market authorisation was initially granted on the basis of the results of studies conducted prior to 2000. In 2000 and later a consensus document of the Joint ESC/American College of Cardiology Committee for the redefinition of MI led to revise the definition of acute coronary syndromes (ACS) which changed to UA and NSTEMI.

The CHMP agreed to use this definition in the enoxaparin labelling, and the indication was harmonised to state "treatment of unstable angina and Non ST-segment elevation myocardial infarction (NSTEMI), administered concurrently with oral acetylsalicylic acid".

Treatment of acute ST-segment elevation myocardial infarction

The pivotal study "Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT) – Thrombolysis in Myocardial Infarction (TIMI) 25 Study" (ExTRACT-TIMI 25 , Antman, 2006) 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.

For the harmonised SmPC the MAH proposed to reflect these study criteria in the indication "Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI)."

The CHMP considered that the proposed wording is in agreement with clinical data and guidelines (IIbB in ESC guidelines 2012, American Heart Association (AHA) 2011) and is therefore acceptable.

Prevention of extracorporeal thrombus during haemodialysis

Prior to the finalisation of the referral, all countries had this indication in the PI, except the Netherlands who did not find the data using the dosing scheme proposed at that 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. Rationale for the harmonised SmPC is to keep indication with the most common wording accepted in the countries.

The CHMP considered that the provided studies were mainly non randomised, open label and uncontrolled with few patients enrolled. However, the available data demonstrated the efficacy of enoxaparin without any safety signal. Moreover, use of enoxaparin in this indication is now recognised and well established.

LMWHs have become the anticoagulants of choice in the EU for routine outpatient haemodialysis sessions, due to the reliability of their clinical effect, and ease of administration.

The indication was therefore harmonised to state prevention of thrombus formation in extra corporeal circulation during haemodialysis.

In summary, the harmonised indications based on the above considerations are as follows:

- 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.
- Treatment of DVT and pulmonary embolism (PE) excluding PE likely to require thrombolytic therapy or surgery.
- Prevention of thrombus formation in extra corporeal circulation during haemodialysis.
- Acute coronary syndrome:
    - Treatment of unstable angina and Non ST-segment elevation myocardial infarction (NSTEMI), administered concurrently 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).

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.2 – Posology and method of administration

Prophylaxis of venous thromboembolic disease 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.

In moderate risk surgery patients, once daily enoxaparin 20 mg (2000 IU)/day starting 2h prior to surgery is as effective and safe as UFH 5000 units twice daily, as demonstrated in clinical studies carried out with enoxaparin.

The CHMP agreed that both patient and condition related issues may contribute to the risk status and noted that most guidelines agree that patients undergoing major orthopaedic or cancer surgery are at high risk for VTE. However, there is not a uniform definition for high risk patients undergoing other procedures. According to the ACCP 2012 guidelines, and International Consensus Statement (Nicolaides, 2013), there are some specific criteria to consider a patient to be at high risk to develop VTE.

Therefore a statement was included to mention that the “individual thromboembolic risk can be estimated using validated risk stratification model”.

In view of the duration of treatment in these patients, the CHMP considered that enoxaparin sodium treatment should be maintained for a minimal period of 7-10 days whatever the recovery status (e.g.

mobility), as this was proven to be effective in the enoxaparin pivotal trials and is recommended in current guidelines.

In view of the minimum treatment duration CHMP found no supportive evidence for continued treatment after discharge from the hospital or after the patient no longer has significantly reduced mobility.

Taking into account the data on prophylaxis in medical patients, it can be argued that patients who are not mobilised after 5-7 days should be treated with continued prophylaxis. Therefore mobility alone can be used to define the duration of prophylaxis.

The CHMP agreed that the tendency towards shorter hospital stays could result in discharge of patients who are not fully mobile yet. Therefore mobility should be referenced and not discharge.

The posology for moderate risk surgery patients should therefore include: “Continue prophylaxis until the patient no longer has significantly reduced mobility” in patients with moderate risk.

For high risk patients such as those undergoing major orthopaedic or general surgery with additional risk factors (e.g., cancer) a higher dose of 40 mg (4000 IU)/day is required. In such cases this dose has been shown to be as effective and safe as UFH 5000 units given three times daily.

In view of timing of the initial dose in high-risk patients, there is no definitive evidence in favour of preoperative or postoperative initiation, as shown in the Strebel meta-analysis (Strebel 2002) comparing pre-and post-operative initiation of therapy.

In view of duration of treatment in this population, the CHMP agreed that the following applies:

- For patients who undergo major orthopaedic surgery an extended thromboprophylaxis up to 5 weeks is recommended.
- For patients with a high VTE risk who undergo abdominal or pelvic surgery for cancer an extended thromboprophylaxis up to 4 weeks is recommended.

This is supported by evidence in the enoxaparin studies, as well as in statements from current guidelines that recommend this necessary duration of prophylactic post-operative treatment.

Specific details on administration in spinal/epidural anaesthesia or lumbar puncture in the prophylaxis of venous thromboembolic disease are described under a separate sub-heading under “method of administration” in this section.

Prophylaxis of venous thromboembolism in medical patients

In terms of dose the MAH proposed 40 mg/day, in line with the results from the MEDENOX study where this was effective, as opposed to the 20 mg/day dose that was not.

The MEDENOX study evaluated Enoxaparin at both 2000 UI and 4000 UI. Only Enoxaparin at 4000 UI demonstrated the efficacy for the prevention of VTE in medical patients. In addition, the mean duration of treatment is 10 day, up to 14 days in the MEDENOX study. The harmonised treatment duration is aligned with the data from the MEDENOX study (6 to 14 days), as there is no evidence that a shorter duration may be effective. At least 6 days should be warranted, whatever the mobility status of the patient.

The ACCP guidelines also recommend treating for up to 14 days. An extended prophylaxis, evaluated in the EXCLAIM study (Turpie 2013), increases bleeding with no benefit. The CHMP considered further that the benefit is not established for a treatment longer than 14 days, which should also be reflected in the harmonised SmPC.

Treatment of DVT and PE

All available studies that compared enoxaparin to UFH in patients with DVT +/- PE (Clinical Study Report ENX388002/PK528, Study CPK2091 (Levine, 1996), Decousus, 1998, Mismetti, 2005, Chong, 2005, Ramacciotti, 2004) have either used the 1.5 mg/kg once daily regimen or the 1 mg/kg BID regimen (except the Merli study 529 (Merli 2001)). All these studies showed each of these regimens to be as effective and safe as UFH.

In addition, the CHMP highlighted that the Einstein-PE study (Einstein-PE investigators, 2012), comparing Rivaroxaban vs enoxaparin in this indication, used enoxaparin at 1 mg BID to provide an adequate anticoagulation status. Of note, the ACCP guideline does not support the once daily regimen as the daily dose is lower compared to the twice daily regimen.

During the procedure, the MAH summarised all data supporting the once daily regimen, including any data regarding treatment with a higher, once daily dose and discussed for which patients this regimen would be appropriate. Regarding the studies presented by the MAH, only the Merli study evaluated the non-inferiority versus UFH of two dose regimens of enoxaparin, i.e. 1mg BID and 1.5 mg QD.

The CHMP therefore considered that only the Merli study addressed benefit/ risk evaluation of the two dose regimens in patients with DVT and PE. The two other studies (Chong, 2005, Ramacciotti 2004) provided by the MAH were performed only in patients with DVT. Yet, the claimed indication is the treatment of deep vein thrombosis (DVT) with or without pulmonary embolism (PE), thus it is not formally the claimed indication. In addition, the Merli study evaluated both dose regimens, allowing an indirect comparison. Therefore, the Merli study appears to be the more relevant to address the benefit/risk of the once daily dose regimen.

As far as the Merli study is concerned, enoxaparin 1.50 mg/kg QD achieved non inferiority as compared to UFH. However, several limitations were highlighted:

There is an increased in VTE and mortality with this dose regimen compared to both UFH and enoxaparin 1 mg/kg BID. Indeed, the treatment difference is +0.2 with enoxaparin QD vs UFH and - 1.2 with enoxaparin BID vs UFH. An indirect comparison of enoxaparin BID and enoxaparin QD shows a treatment difference enoxaparin once a day (QD) - enoxaparin twice a day (BID), IC 95%, 1.5% [-1.5;4.5].

The choice of the non-inferiority margin of 10% is too wide and not justified. The MAH proposed another non inferiority margin of 5% representing a relative increased event rate of almost 200% in the worst case scenario as compare to enoxaparin 1mg/kg BID, which is not acceptable from a clinical point of view. The non-inferiority margin of 5% selected retrospectively is too permissive to conclude the equivalence of enoxaparin 1.5 mg/kg QD vs UFH. To be noticed that in the MATISSE study (Büller et al. 2004) comparing fondaparinux to enoxaparin (1mg/kg BID) in the treatment of DVT, the non-inferiority margin selected was 3.5%.

Considering the Chong study, few patients were enrolled mainly in one country (Australia). This study compared enoxaparin QD vs UFH but also compared outpatient setting vs in hospital setting. There was a high number of non-evaluable patients, and more in the group treated by UFH than enoxaparin (26% vs 17%). In addition, there were more patients with previous DVT in the UFH group (22%) than in the enoxaparin group (17%). The non-inferiority margin is 10%, which is wide and not justified.

Treatment by enoxaparin reduced the recurrence of DVT and PE, significantly with the per protocol analysis but not with all patients treated. There were few patients enrolled and few outcomes in this study. To be noticed that the recurrence of event with enoxaparin are not similar with those already found in the literature.

The Ramacciotti study was performed in one country (Brazil). It is not clear whether this trial assessed superiority or non-inferiority of enoxaparin QD vs UFH. Patients treated with enoxaparin were more likely to be treated at home and the duration of treatment was longer than patient treated in hospital with UFH. This is an important bias. Few patients were enrolled, there were few outcomes and the results are not significant.

Finally, the MAH provided an analysis of a multidisciplinary registry study initiated in March 2001, Computerized Registry of Patients with Venous Thromboembolism (RIETE) enrolling patients with DVT, PE and superficial venous thrombosis, which is not the indication currently discussed. In the RIETE study, there were far more patients treated with the twice daily dose regimen than with the once daily, mainly in Spain. The groups were not identical in terms of risk of VTE and risk of bleeding. In addition, outcomes were evaluated at 15 days and 30 days while VTE are usually evaluated at 3 months or 6 months.

The CHMP concluded that a registry study does not represent the same level of evidence as a prospective randomised study. Therefore, as stated above, only the Merli study allows appreciating the relevance of the once daily dose regimen. This study had several limitations and showed a relative increased event rate of almost 200% in the worst case scenario and an increase in mortality as compared to enoxaparin 1mg/kg BID, which is not acceptable from a clinical point of view.

Of note, the ACCP guideline states that in patients with acute DVT of the leg treated with LMWH, the panel suggests to use once over twice-daily administration (Grade 2C), but they comment that this recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice daily regimen (i.e., the once-daily injection contains double the dose of each twice-daily injection).

Thus, the data suggest at least a trend towards more effect for the BID regimen.

Overall, based on the Merli, Chong and Ramacciotti trials, the once daily treatment regimen can however be considered non-inferior to UFH. It is agreed that the once daily regimen trends to somewhat lesser efficacy compared to BID, but the CHMP considered this would not be reason to remove this option. Bleedings are reduced compared to UFH and maybe on par (Merli) or better (RIETE) compared to the BID regimen.

Once daily treatment is therefore considered an advantage if the prescriber intends to avoid or reduce hospitalisation. This would especially be relevant for patients with uncomplicated disease. In these patients the absolute recurrence risk is low, reducing the potential extra benefit of a slightly superior regimen.

The once daily treatment has been approved in most EU member states. As there is no clear evidence of harm, especially when used cautiously, the CHMP considered that the regimen can be maintained in the SmPC. The CHMP therefore considered that the harmonised wording should include a once daily injection of 150 IU/kg (1.5 mg/kg) or as 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. 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.

Furthermore, the section has been harmonised to reflect that treatment is usually prescribed for an average period of 10 days.

Oral anticoagulant therapy should be initiated when appropriate and enoxaparin sodium treatment should not be discontinued until a therapeutic anticoagulant effect has been achieved. This is further outlined in a separate sub-section on “Switch between enoxaparin sodium and oral anticoagulants”

Prevention of thrombus formation during haemodialysis

In terms of posology, most of the countries state a dose of enoxaparin 1mg/kg and few countries state a lower dose for this indication. Doses studied in the clinical studies vary from 0.5 mg/kg to 1.25 mg/kg. Rationale for the harmonised SmPC is to align the recommended dose as accepted in the most countries which is 1mg/kg. For patients with a high risk of haemorrhage, the dose should be reduced to 0.5 mg/kg for double vascular access or 0.75 mg/kg for single vascular access.

Overall, the CHMP considered that the below harmonised posology is in line with the clinical data and with the current treatment recommendations:

“The recommended dose is 100 IU/kg (1 mg/kg) of enoxaparin sodium.

For patients with a high risk of haemorrhage, 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 haemodialysis, 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 haemodialysis sessions.”

Acute coronary syndrome: treatment of unstable angina and NSTEMI and treatment of acute STEMI

No difference exists between countries in terms of enoxaparin dosage regimen (1 mg/kg every 12 hours by subcutaneous injection) in the unstable angina and NSTEMI indications. However, the CHMP highlighted that in clinical trials, acetylsalicylic Acid (ASA) was administrated at doses from 100 mg to 325 mg. Therefore, to be in line with clinical data and clinical practice, ASA should be recommended at dose from 75 mg to 325 mg in the SmPC. Of note, ASA dosed at 75 mg is available and used by clinicians.

The harmonised wording (in view of NSTEMI) should therefore be as follows:

“Acetylsalicylic acid is recommended for all patients without contraindication at an initial oral loading dose of 150–300 mg (in acetylsalicylic acid-naïve patients) and a maintenance dose of 75–325 mg/day long-term regardless of treatment strategy.”

No disharmony existed in view of the dosage to be used in STEMI, however in terms of the timing of enoxaparin administration in treatment of acute STEMI, since in the pivotal study ExTRACT-TIMI 25, it is specified that in patients younger than 75 years old, enoxaparin had to be given as a fixed IV bolus followed 15 minutes later by the next subcutaneous dose; it is proposed to refer to this timing in the harmonised SmPC.

In terms of the dose and duration of the concomitant aspirin, it is proposed to use the regimen as used in the pivotal ExTRACT-TIMI 25 study (150 to 325 mg of aspirin orally and a maintenance dose after the first 24 hours with 75 to 325 mg for at least 30 days.

The CHMP noted that in the current ESC guideline, Aspirin 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 treatment strategy. For STEMI, the higher dose on the first day as used in ExTRACT-TIMI 25 should be mentioned. The CHMP therefore proposed to align the posology with the ESC guideline.

Overall, based on the above considerations the CHMP agreed to the following harmonised wording for treatment of acute STEMI:

"(…), the recommended dose of enoxaparin sodium is a single intravenous (IV) bolus of 3,000 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 10,000 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.

- For dosage in patients ≥ 75 years of age, see paragraph "Elderly".
- 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."

Paediatric population

No clinical studies assessing the pharmacokinetic (PK), efficacy and safety of enoxaparin sodium in paediatric population were conducted by the MAH. In clinical practice LMWH is commonly used in children with a high risk of thrombosis or an indication for therapeutic anticoagulation. In the literature many studies have been published on the use of LMWH in the paediatric population, including several pharmacokinetic studies (Trame, 2010, Lewis, 2010, Ignjatovic, 2010).

Multiple dose vials and pen containing benzyl alcohol

The CHMP considered further to include a statement regarding benzyl alcohol for multiple dose vials and the pen formulation in line with current guidance on this excipient (Questions and Answers on Benzyl alcohol in the context of the revision of the guideline on 'Excipients in the label 5 and package leaflet of medicinal products for human use (CPMP/463/00)).

Overall, the CHMP considered that the following harmonised wording is appropriate.

"The safety and efficacy of enoxaparin in children have not been established. For multiple dose vials / pen containing benzyl alcohol: Lovenox contains benzyl alcohol and must not be used in new-born and premature neonates (See Section 4.3)."

Elderly

Dosage in this population differed slightly in the terminology between Member States. All MSs made specific recommendations for STEMI in elderly patients above 75 year of age, however not all of the MSs included a statement for other indications.

The clinical data that informs about use in this population originates from the study ExTRACT-TIMI 25. This multicentre clinical trial (CT) performed on patients with STEMI enrolled more than 12% of patients older than 75 years old (1241 patients under enoxaparin and 1291 under UFH). Due to pharmacokinetics studies, the dose was reduced for patients > 75 years old by 25%.

The relative risk (RR) reduction with enoxaparin on the primary endpoint, i.e., death or non-fatal recurrent myocardial infarction, was greater in patients <75 years (20%) than ≥75 years (6%), but the absolute benefits were similar.

For all indications except STEMI, no dose reduction is necessary in the elderly patients, unless kidney function is impaired (see below "renal impairment" and section 4.4).

For treatment of acute STEMI in elderly patients ≥75 years of age, an initial IV bolus must not be used. Initiate dosing with 75 IU/kg (0.75 mg/kg) SC every 12 hours (maximum 75 IU (75 mg) for each of the first two SC doses only, followed by 75 IU/kg (0.75 mg/kg) SC dosing for the remaining doses). For dosage in elderly patients with impaired kidney function, see below "renal impairment" and section 4.4.

The CHMP considered that this dose reduction is recommended in international guidelines and the proposed wording is considered acceptable.

Hepatic impairment

The MAH has not conducted any studies in patients with hepatic impairment, however in literature several studies have been published on the use of LMWH in patients with liver diseases, including pharmacokinetic studies.

Many patients with impaired liver function are at a high risk of thrombosis or have an indication for therapeutic anticoagulation. Therefore the CHMP considered that it would be useful to include information on the pharmacokinetics of enoxaparin in patients with hepatic impairment despite an enhanced risk of bleeding complications. The MAH conducted a literature search on the use of enoxaparin in patients with hepatic impairment during the procedure. Based on the available data, the CHMP agreed to state in this section that

"Limited data are available in patients with hepatic impairment (see section 5.1 and 5.2) and caution should be used in these patients (see section 4.4)."

Renal impairment

This section was harmonised due to different statements and terminology used across Member States for the various degrees of renal impairment.

The CHMP agreed that patients with severe renal impairment are at high risk of bleeding and at high risk of thrombosis. Indeed, Collet (Collet et al. 2005) showed that renal status was an independent predictor of major bleeding and mortality at 30 days (four-fold increased risk in patients with severe renal impairment as compared with patients with normal function). Moreover, multivariable analysis performed by Fox (Fox, 2007), confirmed the effect of a 10 ml/min decrement in creatinine clearance in predicting an increased risk of death, myocardial infarction, stroke, major bleeding. This increased risk of both bleeding and thrombosis related to the renal status should be taken into account in modelling establishing the dose reduction in patients with severe renal impairment.

The CHMP considered that the dose reduction in patients with severe renal impairment proposed by the MAH is only based on PK modelling and not supported by clinical data. The MAH provided post hoc analysis from trials (Fox, 2007, subgroup analysis from ExTRACT TIMI and Collet, 2005 where patients

with severe renal impairment were excluded), and registries studies. These studies compared enoxaparin full dose vs enoxaparin with dose reduction in patients with severe renal impairment, or enoxaparin vs UFH irrespective of the renal status.

The ExCTRACT trial is the only one trial allowing comparison between enoxaparin dose reduced and UFH in 212 patients with severe renal impairment. The reduced dose of enoxaparin did not demonstrate a benefit over UFH while major bleed and intracranial haemorrhage were increased with enoxaparin vs UFH.

A survey of the pharmacovigilance department of the French Health Authority, performed from May 1999 to October 2000, showed an increased risk of bleeding in patients with severe renal impairment and treated by enoxaparin (treatment dose), leading the French agency to contra-indicate the treatment dose regimen of LWMH in this population. This survey concerned all LMWH and was performed in 2000.

The ACCP guidelines (2008 and 2012) recommend to:

- Use UFH over LMWH in patients with severe renal impairment (Grade 2C).
- If LMWH is used in those patients, it is suggested to use 50% of the recommended dose (Grade 2C).

In summary, based the CHMP highlighted the following aspects:

- Enoxaparin is mainly eliminated by the kidney and accumulates with the decline of renal function
- Clinical data in this population are sparse,
- While there are no benefit to use enoxaparin over UFH in patient with severe renal impairment, the risk of bleeding is increased,
- Inability to completely reverse the anticoagulant effects of enoxaparin using protamine when bleeding occurs.

The CHMP therefore considered that:

The efficacy of half dose regimen of enoxaparin needs to be evaluated in each clinical setting, in particular in patients with a high thrombotic risk.

The dose adaptation in subjects with renal impairment depends primarily on PK characteristics. Because renal insufficiency is associated with changes in coagulation activity (mostly related to reduced platelet function), potentially a different level of coagulation could be required.

The MAH's proposal for severe renal insufficiency is based on pharmacokinetic (PK) data and supported by subgroup analyses of the main clinical studies. For mild or moderate renal insufficiency, no additional subgroup data are provided, but current SmPCs are not requiring dose adaptations. This is supported based on PK data.

The contra-indication (in severe renally impaired patients) can be removed, as the MAH could provide reassuring data regarding benefit of half dose of enoxaparin in patients with severe renal impairment during the procedure.

The following dosage table has therefore been included to provide information on dosing in patients with severe renal impairment (creatinine clearance [15-30] ml/min):

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 NSTEMI	100 IU/kg (1 mg/kg) body weight SC once daily
Treatment of acute STEMI (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 STEMI (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

The recommended dosage adjustments do not apply to the haemodialysis indication.

Enoxaparin sodium is however not recommended for patients with end stage renal disease (creatinine clearance <15 ml/min) due to lack of data in this population outside the prevention of thrombus formation in dialysis patients.

Concerning the patients with moderate renal impairment, the CHMP agreed to the following wording for dosage in this patient population:

For moderate and mild renal impairment, the CHMP considered that no further changes are required, and the PI continues to state that although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

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.

As outlined in the previous and the following section, some Member States had a contraindication for severe renal impairment (clearance <30 ml/min) in the treatment 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) outside the prevention of thrombus formation in dialysis patients 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.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.4 – Special warnings and precautions for use

Generally, the proposed information on Special warnings and precautions for use was consistently present in the national SmPCs. The CHMP however agreed with minor modifications to include the proposed labelling for the sub-sections “interchangeability”, “Laboratory tests”, “Percutaneous coronary revascularisation procedures”, “Mechanical prosthetic heart valves”, “Pregnant women with mechanical prosthetic heart valves”, “Low weight”, “Obese Patients”, “Hyperkalaemia”, “Benzyl alcohol” (for multiple dose vials and pen – see also section 4.3 discussed above).

The CHMP however discussed the following points for inclusion in the product information:

The use of enoxaparin sodium in patients with a history of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies is contraindicated. As circulating antibodies may persist several years, the CHMP agreed to reflect this information under the sub-heading “History of HIT” in line with section 4.3 Contra-indication. In addition, enoxaparin sodium is to be used with extreme caution in patients with a history (>100 days) of heparin-induced thrombocytopenia without circulating antibodies. With regards to patients at low risks of HIT, the CHMP also considered necessary to amend the proposed harmonised wording on platelet count monitoring to take into account current international guidelines, in order to avoid unnecessary monitoring in patients at low risk of HIT.

The CHMP agreed to amend the sub-section “elderly” to reflect the need for reduction of dosage in patients above 75 years old treated by enoxaparin for ST-segment elevation myocardial infarction (STEMI) included in section 4.2. Similarly the sub-section “hepatic impairment” was amended to reflect the risk of increase bleeding in hepatic impaired patients included in section 4.2, 5.1 and 5.2 and the sub-section “renal impairment” updated in line with sections 4.2 and 5.2 to advise for consideration of careful biological monitoring by anti-Xa activity measurement and state that Enoxaparin sodium is not recommended for patients with end stage renal disease (creatinine clearance <15 ml/min) due to lack of data in this population outside the prevention of thrombus formation in dialysis patients.

Finally the contra-indication that spinal/epidural anaesthesia or lumbar puncture must not be performed during treatment with enoxaparin at doses used for treatment was also added to section 4.4 accordingly and, in sub-section “haemorrhage”, the increased potential bleeding was added in line with the amendments made to sections 4.2 and 5.2.

The CHMP concurred to add a sub-section “Skin necrosis and cutaneous vasculitis” to reflect that treatment should be discontinued promptly would skin necrosis and cutaneous vasculitis be experienced by the patient as included in section 4.8 of the product information.

Indications for antithrombotic therapy (anticoagulant and antiplatelet agents) are the same in infective endocarditis patients as in the general population. It is known that the management of antithrombotic therapy in patients with infective endocarditis is challenging given the competing risks of embolism and intracerebral haemorrhage in this condition. No data regarding the use of enoxaparin in prophylaxis or treatment of DVT in infective endocarditis population was retrieved from clinical trials as this

population was not included in trials. No published epidemiological studies examining the risk of bleeding and mortality associated with LMWH in infective endocarditis patients were identified.

However, many patients with infective endocarditis have indications for antithrombotic therapy, particularly patients with mechanical prosthetic valves. In such patients the potential risks and benefits of antithrombotic therapy must be carefully weighed. According to the 2015 ESC guidelines on the management of infective endocarditis, the role of bridging therapy from oral anticoagulants to UFH or LMWH may have reasonable advantages in special situations (i.e. in unstable patients) before surgical decisions are made or to avoid drug interactions (Habib, 2015). Consequently, the CHMP considered that the risk of acute infectious endocarditis should be addressed in section 4.4 of the SmPC in order to allow this population to be treated for the prevention of VTE or treatment if necessary and after the benefit risk is considered.

The CHMP agreed to add a generic wording to improve traceability of biological medicinal products as already included in the product information of one MS.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.5 – Interaction with other medicinal products and other forms of interaction

The CHMP agreed with the MAH's approach to use the Stockley's recommendations as well as the guideline on SmPC and categorise the drug-drug interactions already specified in the nationally approved SmPCs according to "contraindicated", "not recommended" and "precaution", completed by a list of examples of thrombolytics. Based on the reviews made, the CHMP notably concluded that: "The cumulative weighted evidence is insufficient to support a drug-drug interaction (DDI) between enoxaparin and antihistamines, digitalis preparations, tetracyclines, nicotine abuse and ascorbic acid."

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.6 – Fertility, pregnancy and lactation

Generally the proposed information on fertility, pregnancy and lactation, when already included in the national SPCs, was consistently present. The CHMP generally agreed with the proposed labelling. The CHMP however discussed the following points for inclusion in the product information:

Pregnancy

The CHMP noted that that the animal studies presented by the MAH did not shown any evidence of foetotoxicity or teratogenicity. In addition, in the pregnant rat, the transfer of 35S-enoxaparin sodium across the maternal placenta to the foetus is minimal. In humans, there was no evidence that enoxaparin sodium crosses the placental barrier during the second and third trimester of pregnancy. However, no information was available concerning the first trimester.

Although a large amount of data is available regarding women exposed to enoxaparin during pregnancy, most of the studies reviewed were not dedicated safety studies and/or the data collected provide little relevant information. In many instances, the exposure period was not mentioned not allowing calculating the number of women exposed during the organogenesis. In other instances, where the neonatal outcome was included in the endpoints, it lacked information to properly assess the neonatal safety. As data indicates no malformative or foetal/neonatal toxicity, the CHMP agreed the data did not suggest any safety signal and the SmPC should be modified accordingly.

In addition, although pregnant women receiving enoxaparin sodium should be carefully monitored for evidence of bleeding or excessive anticoagulation and should be warned of the haemorrhagic risk,

based on the literature data reviewed and on the pharmacovigilance cases from the MAH database, overall, the data currently available suggest that there is no evidence for an increased risk of haemorrhage, thrombocytopenia or osteoporosis with respect to the risk observed in non-pregnant women, other than that observed in pregnant women with prosthetic heart valves (see section 4.4). The CHMP concurred that the majority of the above reported adverse reactions were in accordance with the known safety profile of enoxaparin.

Finally, although not consistently mentioned in national SmPC, the CHMP agreed that recommendation to withdraw heparin treatment before an epidural anaesthesia should be mentioned due to the very frequent use of epidural/spinal anaesthesia in obstetrics.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Breastfeeding

The CHMP noted that in lactating rats, the concentration of 35S-enoxaparin sodium or its labelled metabolites in milk is very low, but although the oral absorption of enoxaparin sodium is unlikely, it is not known whether unchanged enoxaparin sodium is excreted in human breast milk.

However considering:

- the very low passage in rats milk,
- the low passage expected in human milk (due to the physicochemical properties of enoxaparin),
- the small anti-Xa activity expected in human milk (due to the data available for dalteparin[1] describing a low milk/plasma ratio),
- the unlikely oral absorption of enoxaparin by the breastfed children (due to polysaccharide structure of enoxaparin and supported by the study (Guillonneau, 1996) describing no anti-Xa activity in breastfeeding children from mother treated with enoxaparin),
- the probable large use of enoxaparin after caesarean deliveries in women who breastfed their children,

the CHMP considered that enoxaparin sodium can be used during breastfeeding, in line with the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling which states that “conclusions from non-clinical studies on the transfer of the active substance and/or its metabolite(s) into milk should be given when no human data are available.”

Fertility

There are no clinical data for enoxaparin sodium in fertility. Animal studies did not show any effect on fertility (see section 5.3).

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.7 – Effects on ability to drive and use machines

Information in this section consistently reflects across member states that enoxaparin does not affect the ability to drive or use machines.

No changes have been made to the SmPC in this section.

Section 4.8 – Undesirable effects

There were divergences across the national SmPCs in terms of organisation of the information, the adverse drug reactions (ADR) terms and the ADR frequencies:

Organisation of information

The undesirable effects section of the Company Core Data Sheet (CCDS), as well as in the majority of local SmPCs, was organised as follows:

- A part on clinical studies which contains a table on haemorrhage, a table on thrombocytosis and thrombocytopenia and last, a table named "other clinically relevant adverse reactions";
- A second part on post marketing experience.

The MAH updated this section during the procedure in line with the tabular format recommended by the current SmPC guideline. The CHMP further considered that:

- A separate presentation of the three most common events from clinical trials was acceptable for haemorrhages, thrombocytopenia and thrombocytosis. However, those reactions should also be mentioned in the general tabulated table under Blood and lymphatic system disorders SOC, under the frequency 'common';
- a subsection on paediatric population should be added in line with updates to sections 4.3 and 4.4, as follows:

"Paediatric population

The safety and efficacy of enoxaparin sodium in children have not been established (see section 4.2)

Multiple dose vials and Pen containing benzyl alcohol.

The administration of medicinal product containing benzyl alcohol as a preservative to neonates has been associated with a fatal "Gasping Syndrome" (see Section 4.3). Benzyl alcohol may also cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old (see section 4.4)."

Review of ADR terms

No major discrepancy was identified following the review of information contained in the local EU SmPCs. The CHMP however agreed not to include 'false low values for cholesterol,' 'T3/T4 hormones,' 'false high glycaemia,' 'leukopenia' and 'arthralgia' and a class effects of 'unfractionated heparins' and "slight and reversible elevation of platelet count" since there is not enough evidence, at present, to warrant their inclusion.

In addition, the CHMP was in agreement:

- that it was not necessary to specifically describe anaphylactic reactions in detail since they are already detailed in the table of undesirable effects and the signs and symptoms are well known,
- not to include valve thrombosis in patients with prosthetic valves in section 4.8, since prosthetic heart valves thrombosis are related to therapeutic failure rather than being an adverse effect of enoxaparin and considering it is adequately covered in section 4.4:' There have been isolated post-marketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin sodium for thromboprophylaxis'.

- that rare hyperkalaemia being already listed in this section, the additional listing of the underlying mechanism (hyperaldosteronism) was not deemed necessary,
- not to include pulmonary embolism as it is a consequence of lack of efficacy or medication error (dose lower than needed), and
- to include eosinophilia with a frequency rare.

ADR frequencies

The frequency of ADRs was broadly in alignment with the CCDS and there were only isolated discrepancies seen in the frequency category assignation between product information approved nationally. The MAH provided two clinical overviews (dated from 2014 and 2010) aiming to review the frequencies of ADRs listed the CCDS according to the EU SmPC guideline methodology. The CHMP also endorsed the methodology of frequency used: The MAH used the "3/N" rule if a frequency could not be estimated from the available data, including for ADRs included in the label before this rule was in force. Accordingly, all the unobserved ADRs would receive the frequency 'rare' (3 / a total of 15000 patients exposed = 0.02% (≥0.01 and < 0.1 %), including for all ADRs identified during the post marketing surveillance of enoxaparin for which the frequency could not be estimated from the available data.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.9 – Overdose

Generally there were no significant divergences across the national SmPCs.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.1 – Pharmacodynamic properties

Pharmacodynamic effects

Generally, there were no significant divergences across the national SmPCs where the proposed wording was already approved. Several countries did however not display all the pharmacological information in Section 5.1 of their SmPC.

Because neither the distribution of the molecular weight nor the manufacturing method are relevant for clinical practice the CHMP considered that these should be removed. The CHMP also considered that it should be specified that enoxaparin has dissociated antithrombotic and anticoagulant activities through anti Xa ant anti IIa activities, with a ratio of 3.6 of these activities. In addition, the CHMP agreed that the paragraph relating to the structure of the molecule did not add to the information on pharmacodynamic properties and should therefore be deleted.

Clinical efficacy and safety

Although the CHMP broadly agreed with the proposed wording with some minor adjustments, the CHMP agreed to add the occurrence of the composite endpoint at both day 14 and day 30 for the indication treatment of unstable angina and non ST elevation myocardial infarction as well as add the relevant safety information consistently across the indications. In addition, the CHMP requested that the section on treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) is aligned by adding the incidence of bleeding and major bleeding as follows: "The incidence of major bleeding at 30 days was significantly higher ($p<0.0001$) in the enoxaparin sodium group (2.1%) versus the heparin group (1.4%). There was a higher incidence of gastrointestinal bleeding in the enoxaparin sodium

group (0.5%) versus the heparin group (0.1%), while the incidence of intracranial haemorrhage was similar in both groups (0.8% with enoxaparin versus 0.7% with heparin)."

Hepatic impairment

A review of the literature indicated that Enoxaparin is commonly used as anticoagulant in patients with liver cirrhosis mainly to prevent portal vein thrombosis. The use of Enoxaparin in LMWH in cirrhotic patients appears to be effective and safe. The CHMP therefore agreed to update the SmPC section 5.1 with information on liver cirrhosis, and to mention the lowest (4000IU) dose tested in literature studies that was reported to be effective and safe, while reflecting in the PI that the currently available data do not allow formal dosing recommendations (Bechmann, 2010, Shatzel J, 2015, Intagliata NM , 2014, Rodriguez KI, 2011, Cui SB, 2015, Villa E, 2012, European Association for the Study of the Liver Clinical Practice Guidelines: Vasculardiseases of the liver, 2016).

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.2 – Pharmacokinetic properties

Generally there were no significant divergences across the national SmPCs in this section. However, the CHMP considered that the absence of accumulation should be explicitly mentioned in the paragraph on absorption. Several countries did however not display all the pharmacokinetic properties in Section 5.2 of their SmPC.

Although the MAH did not conduct any studies in patients with hepatic impairment, a literature research on the use of enoxaparin in patients with hepatic impairment identified one relevant study (Bechmann, 2010) conducted in patients with cirrhosis. Blood samples for assessment of anti-Xa activity and antithrombin-III level were collected 4 hours after subcutaneous injection on 2 consecutive days. This study showed a significant decrease in anti-Xa activity associated with the increase in the severity of hepatic impairment. Low levels of anti-thrombin, because of reduced synthesis in patients with cirrhosis, are the most likely cause of the phenomenon. Considering the above study and considering that many patients with impaired liver function are at a high risk of thrombosis or have an indication for therapeutic anticoagulation, the CHMP concluded that information on the pharmacokinetics of enoxaparin in patients with hepatic impairment should be added to the PI in line with the corresponding update to section 4.2.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.3 – Preclinical safety data

Generally there were no significant divergences across the national SmPCs where the wording was already approved. Several countries did however not display all the preclinical safety information in Section 5.3 of their SmPC.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 6 – Pharmaceutical particulars

Section 6 has been reworded in order to be in line with the SmPC guideline and to state that enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water (see section 4.2) accordingly.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

2.2.1.2. Package Leaflet (PL)

The PL was amended in accordance with the changes made to the SmPC. The MAH has committed to carry out a user testing on the PL.

2.2.2. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

However, the CHMP was of the opinion that “use in patient with severe renal impairment” and “monitoring of medication errors” should be added to the safety concerns and be closely monitored in the periodic safety update report (PSURs).

Considering the deletion of the contra-indication of use in patients with severe renal impairment and the harmonisation of the way enoxaparin strength are expressed to provide healthcare professionals clarity about enoxaparin doses regardless of the style they are familiar with to avoid medication error leading to risk of thrombosis or major bleeding, whilst keeping mention of the two dose regimens in DVT/PE treatment, the CHMP concluded that the frequency of PSURs should be amended, with the next PSURs to be submitted with a data lock point (DLP) of 3 April 2018, which should be reflected in the EURD list accordingly.

3. Recommendation

Based on the review of all available data the CHMP recommended the revision and harmonisation of the product information for Lovenox and associated names. The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

In addition, taking into account the potential risk of medication errors and the clarification as regards to 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, and 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.

4. Grounds for 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 an 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.

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