RISK MANAGEMENT PLAN - PART VI

SUMMARY OF THE RISK MANAGEMENT PLAN

Active substance(s) (INN or common name)	**Enoxaparin sodium**
Product(s) concerned (Brand name(s))	**CLEXANE®/CLEXANE FORTE®/KLEXANE®/LOVENOX®/ QUALIOP®/ENOXAPARIN SANOFI®/ENOXAPARINE SANOFI®**
Name of Marketing Authorization Holder or Applicant	Sanofi group of companies
Data lock point (DLP) for this module	**17-Nov-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.2**

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ABBREVIATIONS

CHMP:	Committee for Medicinal Products for Human Use
DHPC:	Direct Healthcare Professional Communication
DLP:	Data Lock Point
DVT:	Deep Vein Thrombosis
EU:	European Union
ICSRs:	Individual Case Safety Report
INN:	International Nonproprietary Name
IU:	International Units
PE:	Pulmonary Embolism
PI:	Product Information
PL:	Patient Leaflet
PSUR:	Periodic Safety Update Report
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
STEMI:	ST segment elevation Myocardial Infarction

Summary of Risk Management Plan for

CLEXANE®/CLEXANE FORTE®/KLEXANE®/LOVENOX®/ QUALIOP®/ENOXAPARIN SANOFI®/ENOXAPARINE SANOFI® (Enoxaparin sodium)

This is a summary of the Risk Management Plan (RMP) for CLEXANE/CLEXANE FORTE/KLEXANE/LOVENOX/ QUALIOP/ENOXAPARIN SANOFI/ENOXAPARINE SANOFI. The RMP details important risks about the medicine, how these risks can be minimized, and how more information will be obtained about the medicine's risks and uncertainties (missing information).

The product's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how the medicine should be used.

VI.1. THE MEDICINE AND WHAT IT IS USED FOR

CLEXANE/CLEXANE FORTE/KLEXANE/LOVENOX/QUALIOP/ENOXAPARIN SANOFI/ENOXAPARINE SANOFI is authorized in adults for:

- Prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular those undergoing orthopedic 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 deep vein thrombosis and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery.
- Prevention of thrombus formation in extracorporeal circulation during hemodialysis.
- Acute coronary syndrome:
    - Treatment of unstable angina and non-ST segment elevation myocardial infarction, in combination with oral acetylsalicylic acid.
    - Treatment of acute ST segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention.

It is a solution for injection containing enoxaparin sodium as the active substance and it is given by subcutaneous route or intravenous bolus or extracorporeal use in the dialysis circuit.

VI.2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of CLEXANE/CLEXANE FORTE/KLEXANE/LOVENOX/QUALIOP/ ENOXAPARIN SANOFI/ENOXAPARINE SANOFI's, together with measures to minimize such risks and the proposed studies for learning more about the medicine's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of CLEXANE/CLEXANE FORTE/KLEXANE/LOVENOX/QUALIOP/ ENOXAPARIN SANOFI/ENOXAPARINE SANOFI, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of the medicine is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of the medicine are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of the medicine. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 1 - List of important risks and missing information

Important identified risks	Major hemorrhages Heparin-induced thrombocytopenia
Important potential risk	Medication error (in relation to the double strength expression)
Missing information	Use in patients with hepatic impairment Use in pregnant women and lactating women Use in children and adolescents

II.B Summary of important risks

Table 2

Important identified risk - Major hemorrhages	
Evidence for linking the risk to the medicine	ICSRs and literature
Risk factors and risk groups	Conditions with a high risk of uncontrolled hemorrhage (eg, recent hemorrhagic stroke). Conditions with increased potential for bleeding (impaired hemostasis, history of peptic ulcer, recent ischemic stroke, uncontrolled severe arterial hypertension, diabetic retinopathy, recent neuro- or ophthalmologic surgery). Invasive procedures (eg, percutaneous coronary revascularization procedures, spinal/epidural anesthesia). Concomitant use of medications affecting hemostasis such as salicylates, nonsteroid anti-inflammatory drugs, dextran 40, ticlopidine and clopidogrel, thrombolytics and anticoagulants, other anti-platelet agents including glycoprotein IIb/IIIa antagonists. Renal impairment: there is an increase in exposure of enoxaparin sodium which increases the risk of bleeding. Low weight women (<45 kg) and low weight men (<57 kg), which may lead to a higher risk of bleeding. Elderly patients (especially patients ≥80 years) may be at an increased risk for bleeding complications with the therapeutic dosage ranges.
Risk minimization measures	Routine risk minimization measures: Labeled in sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 5.1 of SmPC Labeled in sections 2, 3 and 4 of PL Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

ICSRs: Individual Case Safety Report; PL: Patient Leaflet; SmPC: Summary of Product Characteristics.

Table 3

Important identified risk: Heparin-induced thrombocytopenia	
Evidence for linking the risk to the medicine	ICSRs and literature
Risk factors and risk groups	Patients with prior history of heparin-induced thrombocytopenia with other heparin-derived compounds are at higher risk. Elderly patients undergoing post-surgical prophylaxis or treatment for DVT, in particular orthopedic and cardiovascular surgery, seem to be at higher risk.
Risk minimization measures	Routine risk minimization measures: Labeled in sections 4.3, 4.4 and 4.8 of SmPC Labeled in section 2 of PL Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

DVT: Deep Vein Thrombosis; ICSR: Individual Case Safety Report; PL: Patient Leaflet; SmPC: Summary of Product Characteristics.

Table 4

Important potential risk: Medication error (in relation to the double strength expression)	
Evidence for linking the risk to the medicine	Prior to the PI harmonization through referral Article 30, depending on the EU member state, the enoxaparin strength was expressed either in mg or in IU of anti-Xa activity. In the frame of the referral Article 30 a harmonized expression of the strength throughout the PI has been adopted. The enoxaparin strength will now be expressed both in IU of anti-Xa activity and in mg. One mg of enoxaparin sodium is equivalent to 100 IU anti-Xa activity. Request from the CHMP to add “monitoring of medication errors” to the safety concerns.
Risk factors and risk groups	None
Risk minimization measures	Routine risk minimization measures: The quantity in mg corresponding to IU given aside throughout the SmPC Additional risk minimization measures: DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

CHMP: Committee for Medicinal Products for Human Use; EU: European Union; IU: International Units; PI: Product Information; DHPC: Direct Healthcare Professional Communication; SmPC: Summary of Product Characteristics.

Table 5

Missing information: Use in patients with hepatic impairment	
Risk minimization measures	Routine risk minimization measures: Labeled in sections 4.2, 4.4 and 5.1 of SmPC Labeled in sections 2 and 4 of PL Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

PL: Patient Leaflet; SmPC: Summary of Product Characteristics.

Table 6

Missing information: **Use in pregnant women and lactating women**	
Risk minimization measures	Routine risk minimization measures: Labeled in sections 4.4 and 4.6 of SmPC Labeled in section 2 of PL Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

PL: Patient Leaflet; SmPC: Summary of Product Characteristics.

Table 7

Missing information: Use in children and adolescents	
Risk minimization measures	Routine risk minimization measures: Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC Labeled in section 3 of PL Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

PL: Patient Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1.Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of CLEXANE/CLEXANE FORTE/KLEXANE/LOVENOX/QUALIOP/ ENOXAPARIN SANOFI/ENOXAPARINE SANOFI's.

II.C.2.Other studies in post-authorization development plan

There are no studies required for CLEXANE/CLEXANE FORTE/KLEXANE/LOVENOX/QUALIOP/ ENOXAPARIN SANOFI/ENOXAPARINE SANOFI's.

REFERENCES

None