RISK MANAGEMENT PLAN SUMMARY

ENOXAPARIN SODIUM

Enoxaparin sodium 2,000 IU (20mg)/0.2 ml solution for injection in prefilled syringes
Enoxaparin sodium 4,000 IU (40mg)/0.4 ml solution for injection in prefilled syringes
Enoxaparin sodium 6,000 IU (60mg)/0.6 ml solution for injection in prefilled syringes
Enoxaparin sodium 8,000 IU (80mg)/0.8 ml solution for injection in prefilled syringes
Enoxaparin sodium 10,000 (100mg)/1 ml solution for injection in prefilled syringes
Enoxaparin sodium 12,000 IU (120 mg)/0.8 mL solution for injection in prefilled syringes
Enoxaparin sodium 15,000 IU (150 mg)/1 mL solution for injection in prefilled syringes

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Marketing Authorisation Holder:	CHEMI S.p.A - Italy

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I. Overview

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Enoxaparin CHEMI is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Enoxaparin CHEMI in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

CHEMI S.p.A is fully responsible for the accuracy and correctness of the content of this published summary RMP of Enoxaparin CHEMI.

II. Summary of the risk management plan for Enoxaparin CHEMI

This is a summary of the Risk Management Plan (RMP) for Enoxaparin CHEMI. The RMP details important risks of Enoxaparin CHEMI, how these risks can be minimised, and how more information will be obtained about Enoxaparin CHEMI risks and uncertainties (missing information).

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

This summary of the RMP for Enoxaparin CHEMI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Enoxaparin CHEMI's RMP.

III. The medicine and what it is used for

Enoxaparin Chemi is authorised in adults for:

- ✓ Prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery.
- ✓ Prophylaxis of venous thromboembolic disease in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infections or rheumatic diseases) and reduced mobility at increased risk of venous thromboembolism
- ✓ Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery.
- ✓ Prevention of thrombus formation in the extracorporeal circulation during haemodialysis.
- ✓ Acute coronary syndrome:

- Treatment of unstable angina and Non ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid.
- Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).

IV. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Enoxaparin Chemi, together with measures to minimise such risks, are outlined below.
Measures to minimise 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

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

IV A: List of important risks and missing information

Important risks of Enoxaparin Chemi are risks that need special risk management activities to further investigate or minimise 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 Enoxaparin Chemi. 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 (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risks	➢ Heparin-induced thrombocytopenia (HIT) ➢ Anaphylactic/anaphylactoid reactions ➢ Haemorrhages ➢ Hyperkalaemia ➢ Liver injury
Important potential risks	➢ Valve thrombosis in patients with prosthetic heart valves ➢ Medication errors ➢ Osteoporosis ➢ Use in severe renal impairment

Summary of safety concerns	
Missing information	➢ Use in paediatric patients ➢ Use in patients with hepatic impairment ➢ Use during pregnancy ➢ Use during lactation ➢ Use in obese patients (BMI > 30 kg/m^2) ➢ Use in patients with end stage renal disease (creatinine clearance <15 mL/min)

IV.B Summary of important risks

IMPORTANT IDENTIFIED RISK

Important identified risk: Heparin-induced thrombocytopenia (HIT)	
Evidence for linking the risk to the medicine	Heparin-induced thrombocytopenia is a potentially devastating immune mediated adverse drug reaction caused by the emergence of antibodies that activate platelets in the presence of heparin. Despite thrombocytopenia, bleeding is rare; rather, HIT is strongly associated with thromboembolic complications involving both the arterial and venous systems.
Risk factors and risk groups	Patients of any age, receiving any type of heparin at any dose by any route of administration, are at risk of developing HIT antibodies. In general, incidence of HIT is greater in post-surgical (cardiac > orthopaedic > vascular > general) versus medical (0.8%) or obstetric patients. In orthopaedic patients given subcutaneous prophylactic heparin, the incidence is approximately 5% with UFH and 0.5% with LMWH. Hospital-wide surveillance studies of 32–36 months suggest that HIT occurred in 1.2% of all patients who received heparin for >4 days. Risk factors suggestive of adverse outcomes in HIT include severity of the thrombocytopenia, and lower platelet counts, which are associated with poor outcome, malignancy, and gender. Females are more likely to suffer thrombotic stroke as an outcome of HIT.
Risk minimisation measures	Routine risk minimisation measures Included in SmPC section 4.3 Warning in SmPC section 4.4 Discussed in SmPC section 4.8 Prescription only medicine

Important identified risk: Anaphylactic/anaphylactoid reactions	
Evidence for linking the risk to the medicine	Clinically, this phenomenon is of relevance because of its increasing incidence and the resulting therapeutic difficulties that arise because several cross-reactions between unfractionated and low-molecular-weight heparins.

Risk factors and risk groups	Delayed hypersensitivity skin reactions have occurred mainly in women. These women were generally postmenopausal, pregnant, or in the *postpartum* period, suggesting a hormonal influence on pathogenesis. About half of these patients also had a history of allergy to unfractionated heparin.
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.8 Prescription only medicine

Important identified risk: Haemorrhages	
Evidence for linking the risk to the medicine	In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients). Like other anticoagulants, enoxaparin should be used with extreme caution in patients with an increased risk of haemorrhage (e.g., bacterial endocarditis; congenital or acquired bleeding disorders; active ulceration and angiodysplastic GI disease; haemorrhagic stroke; recent brain, spinal, or ophthalmic surgery; concomitant platelet inhibitor therapy).
Risk factors and risk groups	Patients with low body-weight (women below 45 kg, men below 57 kg) may be at higher risk of bleeding with prophylactic doses of enoxaparin and require careful monitoring. Enoxaparin sodium, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as: - impaired haemostasis, - history of peptic ulcer, - recent ischemic stroke, - severe arterial hypertension, - recent diabetic retinopathy, - neuro- or ophthalmologic surgery, - concomitant use of medications affecting haemostasis.
Risk minimisation measures	Routine risk minimisation measures Warning in section 4.4 Warning in section 4.5 Discussed in SmPC section 4.8 Prescription only medicine

Important identified risk: Hyperkalaemia	
Evidence for linking the risk to the medicine	Hyperkalaemia related to hypoaldosteronism has been reported in patients treated with low-molecular-weight heparins.

Risk factors and risk groups	Patients with hyperkalaemia may be asymptomatic, or they may report the following symptoms (cardiac and neurologic symptoms predominate): Generalized fatigue Weakness Paresthesias Paralysis Palpitations. Hyperkalaemia can lead to sudden death from cardiac arrhythmias.
Risk minimisation measures	Routine risk minimisation measures Warning in section 4.4 Discussed in SmPC section 4.8 Prescription only medicine

Important identified risk: Liver injury	
Evidence for linking the risk to the medicine	The FAERS database lists hepatic injury in 4 % of all enoxaparin-related AEs.
Risk factors and risk groups	Higher dosage and longer duration of enoxaparin were more likely to lead to liver injury.
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.8 Prescription only medicine

IMPORTANT POTENTIAL RISK

Important potential risk: Valve thrombosis in patients with prosthetic heart valves	
Evidence for linking the risk to the medicine	The majority of the evidence comes from observational studies.
Risk factors and risk groups	In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin sodium (100 IU/kg (1 mg/kg) twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and foetal death. There have been isolated post-marketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin sodium for thromboprophylaxis.
Risk minimisation measures	Routine risk minimisation measures Warning in SmPC section 4.4 Prescription only medicine

Important potential risk: Medication error	
Evidence for linking the risk to the medicine	The anticoagulants cited most frequently in medication error reports are unfractionated heparin, warfarin and enoxaparin. From an analysis of MEDMARX, an Internet-accessible performance-improvement tool designed for hospitals and health systems in the U.S.A., enoxaparin accounted for 1.3-1.9% of all medication errors in the period 2001-2005. According to MEDMARX, in 2005, enoxaparin errors were associated with four patient deaths and two cases of permanent harm.
Risk factors and risk groups	NA
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.2 Discussed in SmPC section 6.6 Prescription only medicine

Important potential risk: Osteoporosis	
Evidence for linking the risk to the medicine	Long-term exposure to treatment and prophylaxis of venous thromboembolism cause a modest but progressive decrease in BMD, more evident in patients on LMWH than on acenocoumarol. It is difficult to assess the true effect of LMWH on fracture healing process. Based on literature research, there are no studies on the role of LMWHs on fracture healing in humans.
Risk factors and risk groups	Unfractionated heparin and LMWHs have been shown to have several harmful effects on bone, causing osteoporosis and enhancing the bone resorption. Moreover, both of them seems to increase calcium loss and reduce bone turnover. However, there are few studies reporting the effects of LMWH on bone repair after fractures.
Risk minimisation measures	Routine risk minimisation measures Listed in SmPC section 4.8 Prescription only medicine

Important potential risk: Use in severe renal impairment	
Evidence for linking the risk to the medicine	In patients with severe renal impairment (creatinine clearance <30 mL/min), the AUC at steady state is significantly increased on average by 65% after repeated SC 4,000 IU (40 mg) once daily doses..

Risk factors and risk groups	Patients with severe renal impairment (creatinine clearance 15-30 mL/min).
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.2 Warning in SmPC section 4.4 Discussed in SmPC section 5.2 Prescription only medicine

MISSING INFORMATION

Missing information: Use in paediatric patients	
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.2 Prescription only medicine

Missing information: Use in patients with hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.2 Warning in SmPC section 4.4 Prescription only medicine

Missing information: Use during pregnancy	
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.6 Discussed in SmPC section 5.3 Prescription only medicine

Missing information: Use during lactation	
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.6 Prescription only medicine

Missing information: Use in obese patients (BMI > 30 kg/m^2)	
Risk minimisation measures	Routine risk minimisation measures Warning in SmPC section 4.4 Discussed in SmPC section 5.2 Prescription only medicine

Missing information: Use in patients with end stage renal disease (creatinine clearance <15 mL/min)	
Risk minimisation measures	Routine risk minimisation measures Discussed in SmPC section 4.2 Warning in SmPC section 4.4 Discussed in SmPC section 5.2 Prescription only medicine

IV.C Post-authorisation development plan

Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Enoxaparin Chemi.

Other studies in post-authorisation development plan

There are no studies required for Enoxaparin Chemi.