Summary of risk management plan for Inhixa / Inhixa Multi (Enoxaparin sodium)

Document Date: 06.08.2020

Based on EU-RMP Version ENOXAP-v3.1-200418

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 minimise them.

The RMP summary of "Inhixa / Inhixa Multi" 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 Inhixa / Inhixa Multi in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. "Mylan Pharma GmbH, Steinhausen" is fully responsible for the accuracy and correctness of the content of the published summary RMP of Inhixa / Inhixa Multi.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

The summary below was prepared based on the information included in Part II, IV and V of the present document.

Summary of safety concerns	
Important identified risks	• Haemorrhages • Heparin induced thrombocytopenia (HIT) • Anaphylactoid and Anaphylactic reactions • Liver injury • Hyperkalaemia
Important potential risks	• Valve thrombosis in patients with prosthetic heart valves • Osteoporosis • Medication errors
Missing information	• Use in paediatric patients • Use in patients with hepatic impairment • Use in patients with end stage renal impairment • Use during pregnancy • Use during lactation • Use in obese patients (BMI > .30kg/m^2)

VI. 1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable

VI. 1.3 Summary of Post authorisation efficacy development plan

Not applicable

VI. 1.4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Haemorrhages	SmPC sections 4.2, 4.3, 4.4, 4.8 and 4.9 PIL sections 2 and 4 *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Heparin induced thrombocytopenia (HIT)	SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 *Other routine risk minimisation measures:* Prescription only medicine Targeted follow-up questionnaire	None proposed
Anaphylactoid and anaphylactic reactions	SmPC sections 4.3, 4.4 and 4.8 PIL section 4 *Other routine risk minimisation measures:* Prescription only medicine Targeted follow-up questionnaire	None proposed
Liver injury	SmPC section 4.8 PIL section 4 *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Hyperkalaemia	SmPC sections 4.4, 4.5 and 4.8 PIL section 4 *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Valve thrombosis in patients with prosthetic valves	SmPC sections 4.4 PIL sections 2 and 4 *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Osteoporosis	SmPC section 4.8 PIL section 4 *Other routine risk minimisation measures:* Prescription only medicine	None proposed

Medication errors	SmPC sections 2, 4.2, 4.3 and 4.4 PIL sections 2, 3 and 6 Labelling *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Use in paediatric patients	SmPC sections 4.2 and 4.8 PIL sections 2 and 3 *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Use in patients with hepatic impairment	SmPC sections 4.2 and 4.4 *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Use in patients with end stage renal impairment	SmPC sections 4.2 and 4.4 *Other routine risk minimisation measures:* Prescription only medicine	
Use during pregnancy	SmPC sections 4.4, 4.6 and 5.3 PIL section 2 *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Use during lactation	SmPC section 4.6 PIL section 2 *Other routine risk minimisation measures:* Prescription only medicine	None proposed
Use in obese patients (BMI> 30kg/m2)	SmPC section 4.4 PIL section 2 *Other routine risk minimisation measures:* Prescription only medicine	None proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is responsible for the death of more than half a million people in Europe each year and is the third leading cause of death from cardiovascular causes only ahead of myocardial infarction and stroke. VTE is a common and potentially avoidable cause of morbidity and mortality in patients hospitalized for acute medical illness.

Despite significant advances in the prevention and treatment of VTE, PE is a common preventable cause of hospital death; without appropriate prophylaxis, 1 in 20 hospitalized medical patients may suffer a fatal PE. Without improvement in the use of VTE prophylaxis in medical patients, unexpected PE will remain a serious problem.

Worldwide, coronary artery disease (CAD) is the single most frequent cause of death. Over seven million people every year die from CAD, accounting for 12.8% of all deaths. Every sixth man and every seventh woman in Europe will die from myocardial infarction. Antithrombotic therapy has become the standard of care in the treatment of **acute coronary syndromes** (ACS). The term 'acute coronary syndrome' covers a range of disorders, including heart attack (myocardial infarction) and unstable angina that are caused by the same underlying problem. **Unstable angina** (UA) is one of the commonest life-threatening medical emergencies. It is also classified as a type of acute coronary syndrome. It can be difficult to distinguish UA from non–Q-wave myocardial infarction. Fifty percent of people with UA will have evidence of myocardial necrosis based on elevated cardiac serum markers such as creatine kinase isoenzyme (CK)-MB and troponin T or I, and thus have a diagnosis of non-ST elevation myocardial infarction.

VI.2.2 Summary of treatment benefits

Inhixa 2,000IU (20mg), 4,000IU (40mg), 6,000IU (60mg), 8,000IU (80mg), 10,000IU (100mg), 12,000IU (120mg), 15,000IU (150mg), 30,000IU (30mg) and 50,000IU (50mg) is solution for injection and contains a medicine called enoxaparin sodium. This belongs to a group of medicines called Low Molecular Weight Heparins.
Enoxaparin works by stopping existing blood clots from getting any bigger and by stopping blood clots forming in the blood.

Enoxaparin can be used to treat blood clots; stop the formation of blood clots forming in blood in the following situations: unstable angina, after an operation or long periods of bed rest due to illness, after a heart attack and stop blood clots forming in the tubes of dialysis machines.

VI.2.3 Unknowns relating to treatment benefits

Enoxaparin use is not recommended in children, as safety and efficacy of this medicinal product have not been established in this population.

Due to limited data in patients with hepatic impairment, caution should be exercised.

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 use during haemodialysis.

In humans, there is no evidence that enoxaparin crosses the placental barrier during the second and third trimester of pregnancy. There is no information available concerning the first trimester. As there are no adequately powered and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the physician has established a clear need.

In lactating rats, the concentration of 35S-enoxaparin or its labelled metabolites in milk is very low. It is not known whether unchanged enoxaparin is excreted in human breast milk. The oral absorption of enoxaparin is unlikely, so enoxaparin can be used during breastfeeding.

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Problem with bleeding too easily *(Haemorrhages)*	In clinical studies, haemorrhages were the most commonly reported reaction. As with other anticoagulants, haemorrhage may occur during enoxaparin therapy in the presence of associated risk factors. Enoxaparin use is contraindicated in patients with active major bleeding and conditions with a high risk of uncontrolled haemorrhage, including recent haemorrhagic stroke. In addition, enoxaparin injection should be used with caution in conditions with increased potential for bleeding, such as: impaired haemostasis, history of peptic ulcer, recent ischaemic stroke, uncontrolled severe arterial hypertension, diabetic retinopathy, recent neuro- or ophthalmologic surgery.	If bleeding occurs, the origin of the bleeding should be investigated and appropriate treatment should be instituted.
A severe decrease in the number of platelets in the blood *(Heparin induced thrombocytopenia (HIT))*	Enoxaparin is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia with or without thrombosis. As there is a risk of antibody-mediated heparin-induced thrombocytopenia also occurring with low molecular weight heparins, regular platelet count monitoring should be considered prior to and during therapy with these agents.	It is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin sodium and then regularly thereafter during the treatment. In practice, if a confirmed significant decrease of the platelet count is observed, enoxaparin sodium treatment must be immediately discontinued and the patient switched to another therapy.

Serious allergic reaction that is rapid in onset (including symptoms such as itchy rash, throat or tongue swelling, shortness of breath, vomiting, lightheadedness, and low blood pressure) *(Anaphylactoid and anaphylactic reactions)*	Anaphylaxis results from the rapid degranulation of mast cells and basophils. The term encompasses reactions that are IgE mediated (anaphylaxis) and those that are non- immunologically mediated (anaphylactoid). There is no clinical relevance between the two types of reaction. Anaphylactic and anaphylactoid reactions including shock have been observed rarely with unfractionated heparin and low molecular weight heparins including enoxaparin.	Anaphylactoid and anaphylactic reactions have been rarely reported. Allergological test allow determining a possible IgE-mediated allergic hypersensitivity.
Liver damage *(Liver injury)*	Hepatic enzymes increase (mainly transaminases > 3 times the upper limit of normality) is a very common adverse reaction of enoxaparin. These usually go back to normal after stopping the use of enoxaparin.	Hepatic enzymes should be monitored. In patients with hepatic insufficiency, enoxaparin should be used with caution.
Elevated concentration of the electrolyte potassium (K^+) in the blood *(Hyperkalaemia)*	Heparin can induce hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or taking diuretics such as spironolactone, triamterene or amiloride.	The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible. However, potassium levels should be monitored especially in patients at risk before starting heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Valve thrombosis in patients with prosthetic heart valves	There are no adequate studies assessing anticoagulant properties of enoxaparin sodium in patients with prosthetic heart valves. There have been reports of isolated cases of valve thrombosis in patients with prosthetic heart valves treated with enoxaparin sodium as thromboprophylaxis. Confounding factors, including underlying diseases and insufficient clinical data, limit the evaluation of these cases. Some of the cases involved the treatment of pregnant women in whom thrombosis led to the death of mother and foetus. Pregnant women with prosthetic heart valves may be at increased risk of thromboembolic events. The use of enoxaparin sodium cannot be recommended for this purpose.
Osteoporosis	Use of low molecular weight heparins over extended periods has been reported to be associated with development of osteopenia. Long term use of enoxaparin (greater than 3 months) may increase the risk of bone thinning (osteoporosis). This adverse reaction has been identified during post-approval use and its frequency cannot be estimated from the available data.
Medication errors	Anticoagulants have been identified as one of the top five drug types associated with patient safety incidents in the United States. In the United Kingdom, anticoagulants are one of the classes of drugs commonly associated with fatal medication errors. The anticoagulants cited most frequently in medication error reports are unfractionated heparin, warfarin and enoxaparin (classified as low molecular weight heparin), according to MEDMARX and a hospital study. Some steps that can be taken to promote safe medication use include: • reading back and verifying medication orders given verbally or over the phone. • asking a colleague to double-check medications when giving high-alert drugs • using an oral syringe to administer oral or NG medications • assessing patients for drug allergies before giving new medications • Be sure to use the safety practices already in place in the hospital

Missing information	
Risk	**What is known**
Use in paediatric patients	The safety and effectiveness of Inhixa in children below the age of 12 years have not been established and therefore its use in children is not recommended. Administration to pre term neonates of Inhixa in vials, containing benzyl alcohol as a preservative, is associated with “gasping syndrome”. Medicinal product in vials may cause toxic and anaphylactoid reactions in infants and children up to 3 years old.
Use in patients with hepatic impairment	In the absence of clinical studies, caution should be exercised in patients with hepatic impairment.
Use in patients with end stage renal impairment	There is no data about use of enoxaparin sodium in patients with end stage renal disease outside the prevention of thrombus formation in dialysis patients.
Use during pregnancy	In humans, there is no evidence that enoxaparin crosses the placental barrier during the second and third trimester of pregnancy. There is no information available concerning the first trimester.
	As there are no adequately powered and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this medicinal product should be used during pregnancy only if the physician has established a clear need. The use of enoxaparin for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study (carried out in Africa) of pregnant women with mechanical prosthetic heart valves given enoxaparin 1 mg/kg bw 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 for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism. Enoxaparin sodium is not recommended for use in pregnant women with prosthetic heart valves.
Use during lactation	In lactating rats, the concentration of ^{35}S-enoxaparin or its labelled metabolites in milk is very low. It is not known whether unchanged enoxaparin is excreted in human breast milk. The oral absorption of enoxaparin is unlikely, so enoxaparin can be used during breastfeeding.
Use in obese patients (BMI>30kg/m^2)	Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (with BMI >30 kg/m^2) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

VI. 2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI. 2.6 Planned post authorisation development plan

Not applicable