Part VI. 2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Enoxaparin sodium is indicated to treat blood clots that are in the veins, prevention of forming of blood clots and stops blood clot forming in the tubes of a dialysis machine (used for people with kidney problems). Unwanted forming of blood clots contributes to significant mortality and morbidity worldwide. More than 200,000 people are admitted annually to hospitals in the USA with venous thrombosis (blood clot that forms within a vein), which is among the top three causes of death related to blood vessel diseases. Blood clots that reach the heart can cause heart attacks. Many heart diseases, e.g. unstable angina (not enough blood gets to the heart) and heart attack are the leading causes of death and morbidity related to the circulatory system in developed countries. Therefore, treatment of blood clots that are in the blood or prevention of blood clot forming is important to manage the diseases mentioned above.

VI.2.2 Summary of treatment benefit

Up to know, enoxaparin sodium is marketed since more than 20 years and has been administered to numerous patients. Its clinical benefits have been proven in several clinical trials and are well-established given the long-term clinical experience.

Prevention of blood clot forming

The clinical efficacy of enoxaparin in prophylaxis of venous thromboembolism (blood clot that forms within a vein) in surgical and medically ill patients has been demonstrated. Enoxaparin has been superiorly shown to reduce the occurrence of blood clots in veins compared to placebo (2% vs 8%) and unfractionated heparin (10% vs 18%) in acute brain attack patients. In addition, enoxaparin therapy was effective in the prevention of blood clot forming after general surgery of moderate severity against placebo (12% vs 5%) and comparable against unfractionated heparin.

Treatment of blood clots

In a small clinical study with 67 patients, enoxaparin was found to be superior to intravenous unfractionated heparin, in preventing clot evolution in hospitalized patients with documented proximal vein thrombosis (blood clot that has formed within a vein).

Outpatient efficacy of enoxaparin to unfractionated heparin was compared in another clinical study with 501 patients, with acute blood clots in the veins, who were treated with either intravenous standard heparin in the hospital or enoxaparin administered primarily at home. Enoxaparin-treated patients were discharged immediately and warfarin was used in both groups. Enoxaparin was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism.

Prevention of blood clot forming during haemodialysis

The studies in the prevention of thrombus formation in the extracorporeal circulation during haemodialysis (a procedure to filter the blood used in patients with kidney problems) showed that single bolus treatment with enoxaparin is safe and effective for chronic haemodialysis. In patients requiring continuous haemodialysis, enoxaparin was found to provide improved mean filter life span in comparison to standard heparin.

The effects of enoxaparin on platelets are less pronounced than those of standard heparin, which results in reduced incidences of characteristic adverse effects of heparin, e.g. heparin-induced decrease of platelets in the blood.

VI.2.3 Unknowns relating to treatment benefits

Data on treatment benefits in children and adolescents are only limited.

Adequate and well-controlled studies with enoxaparin in pregnant women are limited. There are some studies published in the medical scientific literature, which investigated the administration of enoxaparin during pregnancy. A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 haemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal haemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates (Product Information of Clexane and Lovenox). Animal studies have not shown any evidence of foetotoxicity or teratogenicity. In the pregnant rat, the transfer of ^{35}S-enoxaparin across the maternal placenta to the foetus is minimal. In humans, there is no evidence that enoxaparin crosses the placental barrier during the second trimester of pregnancy. There is no information available concerning the first and the third trimesters. It is unknown whether unchanged enoxaparin is excreted in human milk. The oral absorption of enoxaparin is unlikely. Only limited data on the use of enoxaparin in patients with hepatic impairment are available from clinical studies.

However, the physiology of the haemostatic system is closely linked to liver function because the liver parenchymal cells produce most of the factors of the clotting and fibrinolytic systems. Acute or chronic hepatocellular diseases and hepatic failure show various haemostatic abnormalities in the coagulation system, fibrinolytic system, platelets, and the reticuloendothelial system (Wada 2008). These haemostatic alterations concern both pro- and anti-haemostatic pathways, and therefore the net result of the haemostatic unbalance is unclear in each patient. The 9th guide of the ACCP considered patients with liver failure a special population for suffering bleeding adverse reactions associated to anticoagulants when INR >1.5 (Kahn 2012).

To date, insufficient data are available on the pharmacokinetics and efficacy of LMWH in cirrhotic patients. In one study, it was demonstrated for the first time that cirrhotic patients, treated with standard doses of Enoxaparin, fail to reach the recommended anti-Xa levels for prophylactic or therapeutic use. Anti-Xa levels were negatively correlated with the severity of liver disease. In a prospective cohort study, the investigators found significantly more haemorrhagic complications in patients with chronic liver disease (defined as elevated transaminase levels) treated with Enoxaparin (1 mg/kg b.i.d.) compared with those without liver disease. Therefore, monitoring of anti-Xa may be useful in cirrhotic patients, to ensure sufficient anticoagulation by LMWH for prophylactic or therapeutic indications. However, treating cirrhotic patients with higher doses of LMWH might result in an elevated risk of haemorrhage. Nevertheless, it should bear in mind, that monitoring of anti-Xa in cirrhotic patients provides only limited information about the actual efficacy of LMWH and whether standard LMWH doses have to be increased in this population (Bechmann 2011).

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m2) has not been fully determined and there is no consensus for dose adjustment.

The currently used porcine PCR is a qualitative method which is not considered in line with the regulation requesting that the ruminant material should be quantitatively identified in relation to the amount of porcine material present in crude heparin. This deficiency in the porcine PCR method could affects the risk of transmission of TSE-agents. As contaminating ruminant material in crude heparin would not be efficiently detected, a potential risk for infection with TSE-agents cannot be excluded. The sponsor has committed to develop, validate and establish a new quantitative PCR method for determination of porcine origin of crude heparin.

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Bleeding	Enoxaparin reduces the ability of the blood to clot. Therefore, there is an increased risk of bleeding when taking Enoxaparin. Bleeding is more likely to occur as symptom of an overdose.	The effect of enoxaparin can be largely neutralised by the slow intravenous injection of pro-tamine. Furthermore, enoxaparin is to be used with caution in patients with an already increased risk of bleeding.
Heparin-induced reduction of the number of platelets in the blood	Heparin-induced reduction of the number of platelets in the blood is a serious and complication associated with heparins, which leads to both bleeding and clotting complications. As the effects of enoxaparin on platelets are less pronounced than with standard heparin, the incidence of this reaction is reduced with enoxaparin compared to standard heparin.	Enoxaparin is to be used with extreme caution in patients with a history of heparin-induced induced reduction of the number of platelets in the blood. Therapy should be stopped immediately if heparin-induced induced reduction of the number of platelets in the blood occurs.
Allergic reactions including anaphylactoid and anaphylactic reactions	Severe hypersensitivity reactions of the immediate type have been rarely observed with enoxaparin. The exact cause of such severe reactions is not known. However, cross-reactivities between unfractionated heparin and low molecular weight heparins have been observed.	Enoxaparin should be used with extreme caution in patients with a known history of heparin allergy. If physicians and patients are aware of this risk, severe hypersensitivity reactions - should they occur – can quickly be managed by initiation of immediate measures.
Liver injury	Transient increase of liver enzyme values has been observed in patients treated with enoxaparin. In many cases, the patients did not show any clinical symptoms. Liver enzyme values usually improved or returned to normal limits approximately within 14 days after discontinuation of treatment. Isolated cases of cellular liver injury and cholestatic (a condition where bile cannot flow from the	Enoxaparin is to be used with extreme caution in patients with a history of liver damage. Therapy should be stopped immediately if patient suffer symptoms of liver damage.

	liver to the duodenum) liver injury have been reported. However, a clear causal relationship with enoxaparin has not yet been established.	
High blood potassium level	Enoxaparin could produce changes in the potassium levels of the blood. This is more likely to happen in people with kidney problems or diabetes.	Enoxaparin is to be used with caution in patients with history of kidney problem or diabetes, or if they are in treatemnt with drugs that increases potassium levels.

Important potential risks	
Risk	**What is known**
Valve clots in patients with mechanical heart valves	Patients with mechanical heart valve, treatment with Enoxaparin Rovi might not be sufficient to prevent blood clots..
Osteoporosis: bones more likely to break	If Enoxaparin Rovi is used for a long period of time (more than 3 months), it may increase the risk of patients getting a condition called 'osteoporosis'. This is when bones are more likely to break

Missing information	
Risk	**What is known**
Limited information on the safety and efficacy of enoxaparin in pregnant and lactating women	Animal studies have not shown any evidence of developmental toxicity. In humans, there is no evidence that enoxaparin crosses the placental barrier during the second trimester of pregnancy. There is no information available concerning the first and the third trimesters. It is unknown whether unchanged enoxaparin is excreted in human milk. However, the oral absorption of enoxaparin is unlikely.
Limited information on the safety and efficacy of enoxaparin in paediatric patients	Limited information on the efficacy and safety of enoxaparin in paediatric patients
Limited information on the safety and efficacy of enoxaparin in patients with impaired liver function	No data regarding the safety and efficacy of enoxaparin in patients with impaired liver function are available from clinical studies.
Limited information on the safety and efficacy of enoxaparin in overweight patients	Limited information on the efficacy and safety of enoxaparin in overweight patients
Limited information on the quantity of Ruminant DNA	The current used porcine PCR is a qualitative method which is not considered in line with the regulation; the ruminant material

in crude heparin	should be quantitatively identified in relation to the amount of porcine material present in crude heparin.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable. No additional risk minimisation measures are planned.

VI.2.6 Planned post-authorisation development plan

Not applicable. No additional post-authorisation development plan is proposed.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concern	Comment
v1. Initial RMP	1April 2016	Allergic reactions including anaphylactoid and anaphylactic reactions	The previous term has been change, in order to include anaphylactic and anaphylactoid reactions.
		Liver injury	The previous term has been change from potential to identified safety concern
		Osteoporosis	The previous term has been change to cover overall population
V2.0.	22 December 2016	Porcine DNA in crude heparin	New safety concern has been included as missing information

Part VII. Annexes