VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

HIT Type II is an immune-mediated condition which can develop following administration of heparin, an anticoagulant (blood thinner) and is usually manifested by development of thrombocytopenia (a low platelet count) and can lead to thrombosis (abnormal formation of blood clots inside a blood vessel). HIT Type II is caused by the formation of abnormal antibodies that activate platelets. If someone receiving heparin develops a new blood clot or if the platelet count falls, HIT Type II should be suspected and it can be confirmed by specific blood tests.

HIT Type II is reported to occur in 2-5% of adult patients treated with heparin. In children, the incidence of HIT Type II is reported to be 2.3% to 3.7%. Majority of HIT Type II patients who present with low platelets develop Deep vein thrombosis and/or Pulmonary embolism (clot in the lungs) if untreated. Approximately 5-10% of patients with HIT Type II die, usually as a result of thrombotic complications. The risk of developing HIT Type II is higher in surgical patients and if heparin is used for prolonged duration. In addition, females are twice more likely to develop this condition compared to males.

VI.2.2 Summary of treatment benefits

Study ARG-911

The efficacy and safety of argatroban as an anticoagulant in patients with HIT Type II were evaluated in this study. The study was designed as a multicentre, open label, flexible dose (i.e. dose titration), prospective, non-randomized study where the efficacy and safety outcomes were compared with historical controls. 304 patients were included in the treatment group, [HIT (without thrombosis) =160 and HITTS (with thrombosis) =144] and the reference group contained 193 patients (HIT=147, HITTS = 46). Patients were followed for up to 37 days after the therapy. The primary end-point was a composite of three individual endpoints of increasing severity: development of new thrombosis, amputation (all causes) and death (all causes).

Efficacy outcome:

Significant improvement in the composite outcome (death, amputation and thrombosis) at 37 days was observed in the argatroban group compared to historical control group in HIT (25.6% vs 38.8%, p=0.014) and HITTS (43.8 % vs 56.5%, p=0.131)

Study ARG-915

This study was similar to ARG 911 in terms of design and objective. It used the same composite outcome as ARG 911. The historical control group in the ARG 911 was used in this study as well as a reference group. 264 patients were included in the treatment group, [HIT (without thrombosis) =125 and HITTS (with thrombosis) =139] and the reference group contained 193 patients (HIT=146, HITTS = 46). Patients were followed for up to 37 days after the therapy.

Efficacy outcome:

Significant improvement in the composite outcome (death, amputation and thrombosis) at 37 days was observed in the argatroban group compared to historical control group in HIT (25.6% vs 38.8%, p=0.021) and HITTS (41 % vs 56.5%, p=0.067)

The above two studies demonstrated that treatment with argatroban showed statistically significant in the incidence of death, amputation and development of new thrombosis.

VI.2.3 Unknowns relating to treatment benefits

The current evidence suggests that efficacy and safety profile of argatroban is similar across a diverse group of patient populations regardless of age, sex and race.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Bleeding (Haemorrhage)	Argatroban can increase the risk of bleeding. Certain other medications (oral anticoagulants, thrombolytics, antiplatelet drugs) can enhance the blood thinning effect and if used along with argatroban can increase the risk of bleeding.	Blood thinning (anticoagulant) effect of argatroban can be easily monitored by blood test (aPTT) and treating physician can use this information to adjust the dose. Argatroban should be used with caution in disease states where there is an increased danger of bleeding. Argatroban must not be used (contraindicated) in patients with uncontrolled bleeding. Drugs which work by making blood thin should not be use along with argatroban. In addition, argatroban must only be used by trained physicians.
Abnormal liver function	Argatroban is metabolised mainly in liver and excretion of argatroban is slower in patients with liver impairment.	Caution should be exercised in patients with liver impairment and reduced dose is recommended. Argatroban must not be used (contraindicated) in patients with severely impaired liver function.
Cerebral haemorrhage	Argatroban can increase the risk of bleeding. Reports suggest that the treatment with argatroban can increase the risk of	

Risk	What is known	Preventability
	cerebral bleeding. Patients with hypertension, those taking blood thinning medications and those with conditions where risk of bleeding is high are thought to increase the risk of cerebral bleeding. Risk factors for cerebral bleeding should be identified and preventative measures should be applied.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Medication error (underdosing)	MPE has developed argatroban as 'ready to use' formulation which does not require dilution. As argatroban is already available as a concentrate for infusion which needs dilution before infusion, the new 'ready to use' formulation may be mistaken for this formulation. If 'ready to use' formulation is diluted erroneously and then infused to the patient then this may result in 'under dose' and may lead to failure in achieving optimal anticoagulant effect.

Missing information

Risk	What is known
Pregnancy and lactation, effect of exposure of argatroban to foetus in mother's womb	No information is currently available on this subset of patients. Caution should be exercised in pregnant patients. Breast feeding is not recommended while during treatment with argatroban.
Paediatric patients	In Europe, argatroban has not been approved for use in paediatric population but it has been approved in the USA for use in certain paediatric patients. There is limited data regarding the use of argatroban in paediatric patients.

VI.2.5 Summary of risk minimisation measures by safety concern

Argatroban should be used by trained healthcare professional in a suitable healthcare setting. This product has additional risk minimization measures. These additional risk minimisation measures are for the risk which is related to argatroban 'ready to use' formulation:

Safety concern in lay terms (medical term): Medication error (underdosing)

Risk minimisation measure(s): Healthcare professional (HCP) education
Objective and rationale Prescribing physicians and pharmacists to understand the difference between two available formulations of argatroban
Summary description of main additional risk minimisation measures

Risk minimisation measure(s): Healthcare professional (HCP) education
1. Two different formulations will be differentiated by; o Brand name o Pack colour (carton, label and Flip-Off® seal) o Vial size (2.5 ml vs 50 ml) o Specific labelling to differentiate the strength and concentration (1mg/ml vs 100mg/ml) o Package Insert describing 'ready to use' formulation 1mg/ml which does not need dilution prior to administration o External carton size 2. Healthcare Professional education programme
Proposed action: HCP educational materials to be provided to prescribing physicians and pharmacists

VI.2.6 Planned postauthorisation development plan

No post-authorization studies have been planned for this product.

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

Not applicable