VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Bivalirudin is indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.

Bivalirudin is also indicated for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention.

Bivalirudin should be administered with acetylsalicylic acid and clopidogrel.

Percutaneous coronary intervention (PCI)
Coronary reperfusion with primary percutaneous coronary intervention (PCI) improves outcomes in patients with acute ST elevation myocardial infarction (MI), an MI with a new or presumably new left bundle branch block, or a true posterior MI if performed in a timely fashion. Most procedures are now performed with drug-eluting stents, which are associated with a lower rate of restenosis than bare-metal stents. Anticoagulant therapy is always given during percutaneous coronary intervention (PCI), with or without stenting, to prevent acute vessel closure due to thrombosis. Thus, all STEMI patients undergoing primary PCI need to be anticoagulated.

Patients undergoing primary PCI typically receive intravenous unfractionated heparin during the procedure to prevent acute vessel closure due to thrombosis. Heparin monitoring is usually performed via serial monitoring of the activated clotting time (ACT). Careful monitoring of the ACT is important because some patients have persistent thrombin activity despite heparin therapy. A target ACT of 250 to 350 seconds seems to be most often used in interventional practice. However, the heparin regimen should probably be less aggressive (target ACT 200 to 250 seconds) when GP IIb/IIIa inhibitors are used. Careful monitoring of the ACT is important because some patients have persistent thrombin activity despite heparin therapy. ([1],[2],[3])

Unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention
Coronary artery disease (CAD) is the leading cause of death in developed countries. Unstable angina (UA) and the closely related condition non–ST-segment elevation myocardial infarction (NSTEMI) are very common manifestations of this disease. These life-threatening disorders are a major cause of emergency medical care and hospitalizations in developed countries.

Unstable angina/NSTEMI constitutes a clinical syndrome subset of the ACS that is usually, but not always, caused by atherosclerotic CAD and is associated with an increased risk of cardiac death and subsequent MI. In the spectrum of ACS, UA/NSTEMI is defined by electrocardiographic (ECG) ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent). The results of angiographic and angioscopic studies suggest that UA/NSTEMI often results from the disruption or erosion of an atherosclerotic plaque and a subsequent cascade of pathological processes that decrease coronary blood flow. Most patients who die during UA/NSTEMI do so because of sudden death or the development (or recurrence) of acute MI. The efficient diagnosis and optimal management of these patients must derive from information readily available at the time of the initial clinical presentation. The clinical presentation of patients with a life-threatening ACS often overlaps that of patients subsequently found not to have CAD.

UA and NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentations are similar but of differing severity; that is, they differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, most commonly troponin I (TnI), troponin T (TnT), or Creatine Kinase isoenzyme MB (CK-MB). Once it has been established that no biomarker of myocardial necrosis has been released (based on 2 or more samples collected at least 6 h apart, with a reference limit of the 99th percentile of the normal population), the patient with ACS may be considered to have experienced UA, whereas the diagnosis of NSTEMI is established if a biomarker has been released. ([4],[5],[6]).

VI.2.2 Summary of treatment benefits

Bivalirudin, a direct thrombin inhibitor, binds specifically to thrombin at its active catalytic site and at the exosite-1 docking locus. It competitively inhibits thrombin with high affinity and is a short-acting agent, with

a half-life of 25 minutes. Bivalirudin has predictable linear pharmacokinetics and hence does not require laboratory monitoring of blood coagulation parameters.

The role of Bivalirudin in ACS has been studied in several large trials. Considering the comparable efficacy to heparin plus GPI, lower bleeding rates and indeed cost effectiveness; bivalirudin is being increasingly used in ACS, particularly in PPCI for STEMI. In addition, bivalirudin, showed excellent efficacy and safety in those studies that evaluated the role of this drug in patients with non–ST-segment elevation myocardial infarction who were undergoing PCI.

Considering this, bivalirudin represents an attractive option as an antithrombotic agent in the cardiac catheterization laboratory. It has several advantages over heparin, and based upon evidence from many clinical trials, it has been proven to be safer than and at least as effective as heparin in the STEMI, NSTEMI/UA, and elective PCI population.

VI.2.3 Unknowns relating to treatment benefits

There are no or limited data from the use of bivalirudin in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or post-natal development.

Bivalirudin should not be used during pregnancy unless the clinical condition of the woman requires treatment with bivalirudin.

It is unknown whether bivalirudin is excreted in human milk. Bivalirudin should be administered with caution in breast-feeding mothers.

No studies on the effects on the ability to drive and use machines have been performed.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions, (Hypersensitivity including anaphylactic reaction and shock)	Allergic type hypersensitivity reactions were reported uncommonly (≥1/1,000 to ≤1/100) in clinical trials. Anaphylaxis, including anaphylactic shock with fatal outcome has been reported very rarely (≤1/10,000) in post-marketing experience. Treatment-emergent positive bivalirudin antibodies are rare and have not been associated with clinical evidence of allergic or anaphylactic reactions. Caution should be exercised in patients previously treated with lepirudin who had developed lepirudin antibodies.	Preventable. Necessary preparations should be made to deal with allergic type hypersensitivity reactions. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of chest, wheezing, hypotension and anaphylaxis. In the case of shock, the current medical standards for shock treatment should be applied. Caution should be exercised in patients previously treated with lepirudin who had developed lepirudin antibodies. Bivalirudin should be administered by

Risk	What is known	Preventability
		a physician experienced in either acute coronary care or in coronary intervention procedures.
Ischaemic complications (Acute stent thrombosis, Coronary stent thrombosis, Catheter thrombosis, Arteriovenous fistula)	Acute stent thrombosis (<24 hours) has been observed in patients with STEMI undergoing primary PCI and has been managed by Target Vessel Revascularisation (TVR).	Incidence and severity may be reduced. Patients should remain for at least 24 hours in a facility capable of managing ischaemic complications and should be carefully monitored following primary PCI for signs and symptoms consistent with myocardial ischaemia. Bivalirudin should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.
Intra-procedural thrombus formation (Surgical and medical procedure)	Intra-procedural thrombus formation has been observed during gamma brachytherapy procedures with Bivalirudin.	Incidence and severity may be reduced. Bivalirudin should be used with caution during beta brachytherapy procedures. Bivalirudin should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.
Cardiac events (Myocardial infarction, Cardiac tamponade, , Angina pectoris, Ventricular tachycardia) (Cardiac disorders)	Adverse events for bivalirudin from HORIZONS, ACUITY, REPLACE-2 trials and post-marketing experience such as myocardial infarction cardiac tamponade, coronary artery thrombosis, angina pectoris and ventricular tachycardia have been reported as occurring with rare (≥1/10,000) frequency.	Incidence and severity may be reduced. Patients should be carefully monitored following primary PCI for signs and symptoms consistent with myocardial ischaemia. Bivalirudin should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.
Bleeding (Haemorraghe)	Patients must be observed carefully for symptoms and signs of bleeding during treatment particularly if bivalirudin is combined with another anticoagulant. Although most bleeding associated with bivalirudin occurs at the site of arterial puncture in patients undergoing PCI, haemorrhage can occur at any site during therapy.	Incidence and severity may be reduced. Treatment should be stopped if bleeding is observed or suspected. There is no known antidote to bivalirudin, however, bivalirudin is haemo-dialysable. When bivalirudin is combined with a platelet inhibitor or an anti-coagulant

Risk	What is known	Preventability
	Unexplained decreases in haematocrit, haemoglobin or blood pressure may indicate haemorrhage. There is no known antidote to bivalirudin but its effect wears off quickly (T½ is 35 to 40 minutes). <u>Co-administration with platelet inhibitors or anti-coagulants</u> Combined use of anti-coagulant medicinal products can be expected to increase the risk of bleeding. In patients taking warfarin who are treated with bivalirudin, International Normalised Ratio (INR) monitoring should be considered to ensure that it returns to pre-treatment levels following discontinuation of bivalirudin treatment. Adverse events for bivalirudin from HORIZONS, ACUITY, REPLACE-2 trials and post-marketing experience such as gastrointestinal haemorrhage (including haematemesis, malaena, oesophageal haemorrhage), Retroperitoneal haemorrhage, Peritoneal haemorrhage, Retroperitoneal haematoma and pharyngeal haemorrhage are included in Section 4. 8 Undesirable effects as occurring with uncommonly (≥1/1,000) frequency. Pulmonary haemorrhage, pericardial haemorrhage and intracranial haemorrhage are also included in this section as occurring with rare (≥1/10,000) frequency.	medicine, clinical and biological parameters of haemostasis should be regularly monitored. Bivalirudin should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.
Reaction in the injection site	Injection site discomfort, pain or local reactions occur in rare occasions with bivalirudin.	Bivalirudin should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.
Use in partients with renal and haepatic impairment	Bivalirudin is contraindicated in patients with severe renal insufficiency and also in dialysis-dependent patients. Caution should be exercised in the elderly due to age-related decrease in renal function. No dose adjustment is needed in patients with abnormal liver functions.	Patients with renal impairment should be monitored. Bivalirudin should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.

Risk	What is known	Preventability
Medication errors (including not compliance with administration method)	Bivalirudin is administered as a weight based regimen consisting of an initial bolus (by rapid IV push) followed by an IV infusion.	Bivalirudin should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.

Important potential risks

Risk	What is known
Interaction with other medicinal products according to the mechanism of action of Bivalirudin	Interaction studies have been conducted with platelet inhibitors, including acetylsalicylic acid, ticlopidine, clopidogrel, abciximab, eptifibatide, or tirofiban. The results do not suggest pharmacodynamic interactions with these medicinal products. From the knowledge of their mechanism of action, combined use of anti-coagulant medicinal products (heparin, warfarin, thrombolytics or antiplatelet agents) can be expected to increase the risk of bleeding. In any case, when bivalirudin is combined with a platelet inhibitor or an anticoagulant medicine, clinical and biological parameters of haemostasis should be regularly monitored.

Missing information

Risk	What is known
Use during pregnancy and breast-feeding	There are no limited data from the use of bivalirudin in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or post-natal development. Bivalirudin should not be used during pregnancy unless the clinical condition of the woman requires treatment with bivalirudin. It is unknown whether bivalirudin is excreted in human milk. Bivalirudin should be administered with caution in breast-feeding mothers.
Use of Bivalirudin in paediatric patients	There are no relevant indication for the use of bivalirudin in children less than 18 years old.
Effects on ability to drive and use machines.	No studies on the effects on the ability to drive and use machines have been performed.

VI.2.5 Summary of risk minimisation measures by safety concern

Each medicinal product has a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicinal product, and the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package information leaflet (PIL). Measures included in these documents are known as routine risk minimisation measures.

These medicinal products have no additional risk minimisation measures. Routine pharmacovigilance should be sufficient for post-marketing safety monitoring of the risks.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

SUMMARY OF CHANGES TO THE RMP		
DATE	**VERSION NUMBER**	**CHANGES**
March 2015	01	As per RMS preliminary assessment report, the following changes to the RMP have been addressed: 1. The risks have been listed individyally in terms of their preferred terms instead of classifying by SOC. 2. The safety concern *Injection site reactions* was added. 3. The safety concern *Use in patient with renal or haepatic impairment* was added. 4. The safety concerns pertaining to different SOCs that reported haemorrhage in several locations were abridged into one safety concern: *Haemorrhage*. 5. The safety concerns that reported thrombosis have been expanded to specifically state "Thrombosis, in particular acute stent thrombosis in patients with STEMI undergoing primary PCI" 6. The safety concern *Medication errors (including reports describing patients receiving bivalirudin bolus without subsequent infusion)* has been added. 7. The safety concern *Use of bivalirudin in paediatric patients has been added.* 8. Missing information regarding the use of the product during pregnancy and breast-feeding were unified in one safety concern. 9. The summary of safety concerns (VI.2.4) was revised to reflect the updated list of safety concerns in the RMP. 10. Additional risk minimisation measures were included. 11. Effectiveness of risk minimisation measures was included. 12. Annex 10 has been updated with details on proposed additional risk minimisation measures. 13. Annex 11 has been updated with mock-up proposal of additional risk minimisation measures. Additionally, references to wording from Section 2.5.5 Overview of Safety from the Common Technical Document was removed from the summary of risk minimisation measures tables, as per other Regulatory Authorities requirement as a result of other RMP assessment procedures. The CTD is a regulatory document, and is not expected to be used by healthcare professionals to minimise the risks associated with use of Bivalirudin.