Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bivalirudin Cipla 250 mg powder for concentrate for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mg bivalirudin

After reconstitution 1 ml contains 50 mg bivalirudin.

After dilution 1 ml contains 5 mg bivalirudin.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for injection/infusion

White to off white lyophilized powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bivalirudin Cipla 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 Cipla 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 Cipla should be administered with acetylsalicylic acid and clopidogrel.

4.2 Posology and method of administration

Bivalirudin Cipla should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.

Posology

Patients undergoing PCI, including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI

The recommended dose of bivalirudin for patients undergoing PCI is an intravenous bolus of 0.75 mg/kg body weight followed immediately by an intravenous infusion at a rate of 1.75 mg/kg body weight/hour for at least the duration of the procedure. The infusion of 1.75 mg/kg body weight/hour may be continued for up to 4 hours post-PCI and at a reduced dose of 0.25 mg/kg body weight/hour for an additional 4-12 hours as clinical necessary. In STEMI patients the infusion of 1.75 mg/kg body weight/hour should be continued for up to 4 hours post-PCI and continued at a reduced dose of 0.25 mg/kg body weight/hour for an additional 4 – 12 hours as clinically necessary (see section 4.4).

Patients should be carefully monitored following primary PCI for signs and symptoms consistent with myocardial ischaemia.

Patients with unstable angina/non-ST segment elevated myocardial infarction (UA/NSTEMI)

The recommended starting dose of bivalirudin for medically managed patients with acute coronary syndrome (ACS) is an intravenous bolus of 0.1 mg/kg followed by an infusion of 0.25 mg/kg/h. Patients who are to be medically managed may continue the infusion of 0.25 mg/kg/h for up to 72 hours.

If the medically managed patient proceeds to PCI, an additional bolus of 0.5 mg/kg of bivalirudin should be administered before the procedure and the infusion increased to 1.75 mg/kg/h for the duration of the procedure.

Following PCI, the reduced infusion dose of 0.25 mg/kg/h may be resumed for 4 to 12 hours as clinically necessary.

For patients who proceed to coronary artery bypass graft (CABG) surgery off pump, the intravenous infusion of bivalirudin should be continued until the time of surgery. Just prior to surgery, a 0.5 mg/kg bolus dose should be administered followed by a 1.75 mg/kg/h intravenous infusion for the duration of the surgery.

For patients who proceed to CABG surgery on pump, the intravenous infusion of bivalirudin should be continued until 1 hour prior to surgery after which the infusion should be discontinued and the patient treated with unfractionated heparin (UFH).

To ensure appropriate administration of bivalirudin, the completely dissolved, reconstituted and diluted product should be thoroughly mixed prior to administration (see section 6.6). The bolus dose should be administered by a rapid intravenous push to ensure that the entire bolus reaches the patient before the start of the procedure.

Intravenous infusion lines should be primed with bivalirudin to ensure continuity of drug infusion after delivery of the bolus.

The infusion dose should be initiated immediately after the bolus dose is administered, ensuring delivery to the patient prior to the procedure, and continued uninterrupted for the duration of the procedure. The safety and efficacy of a bolus dose of bivalirudin without the subsequent infusion has not been evaluated and is not recommended even if a short PCI procedure is planned.

An increase in the activated clotting time (ACT) may be used as an indication that a patient has received bivalirudin.

ACT values 5 minutes after bivalirudin bolus average 365 +/- 100 seconds. If the 5-minute ACT is less than 225 seconds, a second bolus dose of 0.3 mg/kg should be administered.

Once the ACT value is greater than 225 seconds, no further monitoring is required provided the 1.75 mg/kg/h infusion dose is properly administered.

Where insufficient ACT increase is observed, the possibility of medication error should be considered, for example inadequate mixing of bivalirudin or intravenous equipment failures.

The arterial sheath can be removed 2 hours after discontinuation of the bivalirudin infusion without anticoagulation monitoring.

Use with other anticoagulant therapy

In STEMI patients undergoing primary PCI, standard pre-hospital adjunctive therapy should include clopidogrel and may include the early administration of UFH (see section 5.1).

Patients can be started on bivalirudin 30 minutes after discontinuation of unfractionated heparin given intravenously, or 8 hours after discontinuation of low molecular weight heparin given subcutaneously.

Bivalirudin can be used in conjunction with a GP IIb/IIIa inhibitor. For further information regarding the use of bivalirudin with or without a GP IIb/IIIa inhibitor, please see section 5.1.

Renal impairment

Bivalirudin is contraindicated in patients with severe renal insufficiency (GFR<30 ml/min) and also in dialysis-dependent patients (see section 4.3).

In patients with mild or moderate renal insufficiency, the ACS dose (0.1 mg/kg bolus/0.25 mg/kg/h infusion) should not be adjusted.

Patients with moderate renal impairment (GFR 30-59 ml/min) undergoing PCI (whether being treated with bivalirudin for ACS or not) should receive a lower infusion rate of 1.4 mg/kg/h. The bolus dose should not be changed from the posology described under ACS or PCI above.

Patients with renal impairment should be carefully monitored for clinical signs of bleeding during PCI, as clearance of bivalirudin is reduced in these patients (see section 5.2).

If the 5-minute ACT is less than 225 seconds, a second bolus dose of 0.3 mg/kg should be administered and the ACT re-checked 5 minutes after the administration of the second bolus dose.

Where insufficient ACT increase is observed, the possibility of medication error should be considered, for example inadequate mixing of bivalirudin or intravenous equipment failures.

Hepatic impairment

No dose adjustment is needed. Pharmacokinetic studies indicate that hepatic metabolism of bivalirudin is limited, therefore the safety and efficacy of bivalirudin have not been specifically studied in patients with hepatic impairment.

Elderly population

Increased awareness due to high bleeding risk should be exercised in the elderly because of age-related decrease in renal function. Dose adjustments for this age group should be on the basis of renal function.

Paediatric patients

There is currently no indication for the use of bivalirudin in children less than 18 years old and no recommendation on a posology can be made. Currently available data are described in sections 5.1 and 5.2.

Method of administration

Bivalirudin Cipla is intended for intravenous use.

Bivalirudin should be initially reconstituted to give a solution of 50 mg/ml bivalirudin. Reconstituted material should then be further diluted in a total volume of 50 ml to give a solution of 5 mg/ml bivalirudin.

Reconstituted and diluted product should be thoroughly mixed prior to administration.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Bivalirudin is contraindicated in patients with:

- a known hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to hirudins
- active bleeding or increased risk of bleeding because of haemostasis disorders and/or irreversible coagulation disorders
- severe uncontrolled hypertension
- subacute bacterial endocarditis

- severe renal impairment (GFR<30 ml/min) and in dialysis-dependent patients

4.4 Special warnings and precautions for use

Bivalirudin is not intended for intramuscular use. Do not administer intramuscularly.

Haemorrhage

Patients must be observed carefully for symptoms and signs of bleeding during treatment particularly if bivalirudin is combined with another anticoagulant (see section 4.5). 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. Unexplained decreases in haematocrit, haemoglobin or blood pressure may indicate haemorrhage. Treatment should be stopped if bleeding is observed or suspected.

There is no known antidote to bivalirudin but its effect wears off quickly ($T_{1/2}$ is 35 to 40 minutes).

Prolonged post PCI infusions of bivalirudin at recommended doses have not been associated with an increased rate of bleeding (see section 4.2).

Co-administration with platelet inhibitors or anti-coagulants

Combined use of anti-coagulant medicinal products can be expected to increase the risk of bleeding (see section 4.5). When bivalirudin is combined with a platelet inhibitor or an anti-coagulant medicine, clinical and biological parameters of haemostasis should be regularly monitored.

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.

Hypersensitivity

Allergic type hypersensitivity reactions were reported uncommonly (≥1/1,000 to ≤1/100) in clinical trials. Necessary preparations should be made to deal with this. 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. Anaphylaxis, including anaphylactic shock with fatal outcome has been reported very rarely (≤1/10,000) in post-marketing experience (see section 4.8).

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.

Acute stent thrombosis

Acute stent thrombosis (<24 hours) has been observed in patients with STEMI undergoing primary PCI and has been managed by Target Vessel Revascularisation (TVR) (see sections 4.8 and 5.1). The majority of these cases were non-fatal. This increased risk of acute stent thrombosis was observed during the first 4 hours following the end of the procedure among patients who either discontinued the infusion of bivalirudin at the end of the procedure or received a continued infusion at the reduced dose of 0.25 mg/kg/h (see section 4.2).

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.

Brachytherapy

Intra-procedural thrombus formation has been observed during gamma brachytherapy procedures with bivalirudin.

Bivalirudin should be used with caution during beta brachytherapy procedures.

Excipient

Bivalirudin contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

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, clinical and biological parameters of haemostasis should be regularly monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 (see section 5.3).

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

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Bivalirudin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

- The most frequent serious and fatal adverse reactions are major haemorrhage (access site and non access-site bleeding, including intracranial haemorrhage) and hypersensitivity, including anaphylactic shock. Coronary artery thrombosis and coronary stent thrombosis with myocardial infarction, and catheter thrombosis have each been reported rarely. Administration errors may lead to fatal thrombosis.
- In patients receiving warfarin, INR is increased by administration of bivalirudin.

Tabulated list of adverse reactions

Adverse reactions for bivalirudin from HORIZONS, ACUITY, REPLACE-2 trials and post-marketing experience are listed by system organ class in Table 1.

Table 1. Adverse reactions for bivalirudin from HORIZONS, ACUITY, REPLACE-2 trials and post-marketing experience

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)
Blood and lymphatic system disorders		Haemoglobin decreased	Thrombocytopenia Anaemia	INR increased [d]	
Immune system disorders			Hypersensitivity, including anaphylactic reaction and shock, including reports with fatal outcome		
Nervous system disorders			Headache	Intracranial haemorrhage	
Eye disorders				Intraocular haemorrhage	
Ear and labyrinth disorders				Ear haemorrhage	
Cardiac disorders				Myocardial infarction, Cardiac tamponade, Pericardial haemorrhage, Coronary artery thrombosis, Angina pectoris. Bradycardia, Ventricular tachycardia Chest pain	
Vascular disorders	Minor haemorrhage at any site	Major haemorrhage at any site including reports with fatal outcome	Haematoma, Hypotension	Coronary stent thrombosis including reports with fatal outcome[c] Thrombosis including reports with fatal outcome, Arteriovenous fistula, Catheter thrombosis, Vascular pseudoaneurysm	Compartment syndrome[a, b]
Respiratory, thoracic and			Epistaxis, Haemoptysis,	Pulmonary haemorrhage	

mediastinal disorders			Pharyngeal haemorrhage	Dyspnoea[a]	
Gastrointestinal disorders			Gastrointestinal haemorrhage (including haematemesis, melaena, oesophageal haemorrhage, anal haemorrhage), Retroperitoneal haemorrhage, Gingival haemorrhage, Nausea	Peritoneal haemorrhage, Retroperitoneal haematoma, Vomiting	
Skin and subcutaneous tissue disorders		Ecchymosis		Rash, Urticaria	
Musculoskeletal and connective tissue disorders				Back pain, Groin pain	
Renal and urinary disorders			Haematuria		
General disorders and administration site conditions		Access site haemorrhage, Vessel puncture site haematoma ≥5 cm, Vessel puncture site haematoma <5 cm		Injection site reactions (Injection site discomfort, Injection site pain, Puncture site reaction)	
Injury, poisoning and procedural complications				Reperfusion injury (no or slow reflow), Contusion	

[a] ADRs identified in post-marketing experience

[b] Compartment syndrome has been reported as a complication of forearm haematoma following administration of bivalirudin via the radial access route in post-marketing experience

[c] Further detail regarding stent thrombosis is provided in section 4.8: The HORIZONS Trial (Patients with STEMI undergoing primary PCI). For instructions for monitoring acute stent thrombosis, see section 4.4.

[d] Section 4.4 describes precautions for INR monitoring when bivalirudin is co-administered with warfarin.

Description of selected adverse reactions

Haemorrhage

In all clinical studies bleeding data were collected separately from adverse reactions and are summarised in Table 6 together with the bleeding definitions used for each study.

The HORIZONS Trial (Patients with STEMI undergoing primary PCI)

Platelets, bleeding and clotting

In the HORIZONS study both major and minor bleeding occurred commonly (≥1/100 and <1/10). The incidence of major and minor bleeding was significantly less in patients treated with bivalirudin versus patients treated with heparin plus a GP IIb/IIIa inhibitor. The incidence of major bleeding is shown in Table 6. Major bleeding occurred most frequently at the sheath puncture site. The most frequent event was a haematoma <5 cm at puncture site.

In the HORIZONS study, thrombocytopenia was reported in 26 (1. 6%) of bivalirudin-treated patients and in 67 (3.9%) of patients treated with heparin plus a GP IIb/IIIa inhibitor. All of these bivalirudin-treated patients received concomitant acetylsalicylic acid, all but 1 received clopidogrel and 15 also received a GP IIb/IIIa inhibitor.

The ACUITY Trial (*Patients with unstable angina/non-ST segment elevated myocardial infarction (UA/NSTEMI))*

The following data are based on a clinical study of bivalirudin in 13,819 patients with ACS; 4,612 were randomised to bivalirudin alone, 4,604 were randomised to bivalirudin plus GP IIb/IIIa inhibitor and 4,603 were randomised to either unfractionated heparin or enoxaparin plus GP IIb/IIIa inhibitor.

Adverse reactions were more frequent in females and in patients more than 65 years of age in both the bivalirudin and the heparin-treated comparator groups compared to male or younger patients.

Approximately 23.3% of patients receiving bivalirudin experienced at least one adverse event and 2.1% experienced an adverse reaction. Adverse event reactions for bivalirudin are listed by system organ class in Table 1.

Platelets, bleeding and clotting

In ACUITY, bleeding data were collected separately from adverse reactions.

Major bleeding was defined as any one of the following: intracranial, retroperitoneal, intraocular, access site haemorrhage requiring radiological or surgical intervention, ≥5 cm diameter haematoma at puncture site, reduction in haemoglobin concentration of ≥4 g/dl without an overt source of bleeding, reduction in haemoglobin concentration of ≥3 g/dl with an overt source of bleeding, re-operation for bleeding or use of any blood product transfusion. Minor bleeding was defined as any observed bleeding event that did not meet the criteria as major. Minor bleeding occurred very commonly (≥1/10) and major bleeding occurred commonly (≥1/100 and <1/10).

Major bleeding rates are shown in Table 6 for the IIT population and Table 7 for the per protocol population (patients receiving clopidogrel and acetylsalicylic acid). Both major and minor bleeds were significantly less frequent with bivalirudin alone than the heparin plus GP IIb/IIIa inhibitor and bivalirudin plus GP IIb/IIIa inhibitor groups. Similar reductions in bleeding were observed in patients who were switched to bivalirudin from heparin-based therapies (N = 2,078).

Major bleeding occurred most frequently at the sheath puncture site. Other less frequently observed bleeding sites with greater than 0.1% (uncommon) bleeding included “other” puncture site, retroperitoneal, gastrointestinal, ear, nose or throat.

Thrombocytopenia was reported in 10 bivalirudin-treated patients participating in the ACUITY study (0.1%). The majority of these patients received concomitant acetylsalicylic acid and clopidogrel, and 6 out of the 10 patients also received a GP IIb/IIIa inhibitor. Mortality among these patients was nil.

The REPLACE-2 Trial *(Patients undergoing PCI)*

The following data is based on a clinical study of bivalirudin in 6,000 patients undergoing PCI, half of whom were treated with bivalirudin (REPLACE-2). Adverse events were more frequent in females and in patients more than 65 years of age in both the bivalirudin and the heparin-treated comparator groups compared to male or younger patients.

Approximately 30% of patients receiving bivalirudin experienced at least one adverse event and 3% experienced an adverse reaction. Adverse reactions for bivalirudin are listed by system organ class in Table 1.

Platelets, bleeding and clotting

In REPLACE-2, bleeding data were collected separately from adverse events. Major bleeding rates for the intent-to-treat trial population are shown in Table 6.

Major bleeding was defined as the occurrence of any of the following: intracranial haemorrhage, retroperitoneal haemorrhage, blood loss leading to a transfusion of at least two units of whole blood or packed red blood cells, or bleeding resulting in a haemoglobin drop of more than 3 g/dl, or a fall in haemoglobin greater than 4 g/dl (or 12% of haematocrit) with no bleeding site identified. Minor haemorrhage was defined as any observed bleeding event that did not meet the criteria for a major haemorrhage. Minor bleeding occurred very commonly (≥1/10) and major bleeding occurred commonly (≥1/100 and <1/10).

Both minor and major bleeds were significantly less frequent with bivalirudin than the heparin plus GP IIb/IIIa inhibitor comparator group. Major bleeding occurred most frequently at the sheath puncture site. Other less frequently observed bleeding sites with greater than 0.1% (uncommon) bleeding included “other” puncture site, retroperitoneal, gastrointestinal, ear, nose or throat.

In REPLACE-2 thrombocytopenia occurred in 20 bivalirudin-treated patients (0.7%). The majority of these patients received concomitant acetylsalicylic acid and clopidogrel, and 10 out of 20 patients also received a GP IIb/IIIa inhibitor. Mortality among these patients was nil.

Acute cardiac events

The HORIZONS Trial *(Patients with STEMI undergoing primary PCI)*

The following data are based on a clinical study of bivalirudin in patients with STEMI undergoing primary PCI; 1,800 patients were randomised to bivalirudin alone, 1,802 were randomised to heparin plus GP IIb/IIIa inhibitor. Serious adverse reactions were reported more frequently in the heparin plus GP IIb/IIIa group than the bivalirudin treated group.

A total of 55.1% of patients receiving bivalirudin experienced at least one adverse event and 8.7% experienced an adverse drug reaction. Adverse drug reactions for bivalirudin are listed by system organ class in Table 1.The incidence of stent thrombosis within the first 24 hours was 1.5% in patients receiving bivalirudin versus 0.3% in patients receiving UFH plus GP IIb/IIIa inhibitor (p=0.0002). Two deaths occurred after acute stent thrombosis, 1 in each arm of the study. The incidence of stent thrombosis between 24 hours and 30 days was 1. 2% in patients receiving bivalirudin versus 1.9% in patients receiving UFH plus GP IIb/IIIa inhibitor (p=0.1553). A total of 17 deaths occurred after subacute stent thrombosis, 3 in the bivalirudin arm and 14 in the UFH plus GP IIb/IIIa arm. There was no statistically significant difference in the rates of stent thrombosis between treatment arms at 30 days (p=0.3257) and 1 year (p=0.7754).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Cases of overdose of up to 10 times the recommended dose have been reported in clinical trials. Single bolus doses of bivalirudin up to 7.5 mg/kg have also been reported. Bleeding has been observed in some reports of overdose.

In cases of overdose, treatment with bivalirudin should be immediately discontinued and the patient monitored closely for signs of bleeding.

In the event of major bleeding, treatment with bivalirudin should be immediately discontinued. There is no known

antidote to bivalirudin, however, bivalirudin is haemo-dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, Direct thrombin inhibitors, ATC code: B01AE06.

Mechanism of action

Bivalirudin Cipla contains bivalirudin, a direct and specific thrombin inhibitor that binds both to the catalytic site and the anion-binding exosite of fluid-phase and clot-bound thrombin.

Thrombin plays a central role in the thrombotic process, acting to cleave fibrinogen into fibrin monomers and to activate Factor XIII to Factor XIIIa, allowing fibrin to develop a covalently cross-linked framework that stabilises the thrombus. Thrombin also activates Factors V and VIII, promoting further thrombin generation, and activates platelets, stimulating aggregation and granule release.

Bivalirudin inhibits each of these thrombin effects.

The binding of bivalirudin to thrombin, and therefore its activity, is reversible as thrombin slowly cleaves the bivalirudin, Arg_3-Pro_4, bond, resulting in recovery of thrombin active site function. Thus, bivalirudin initially acts as a complete non-competitive inhibitor of thrombin, but transitions over time to become a competitive inhibitor enabling initially inhibited thrombin molecules to interact with other clotting substrates and to coagulation if required.

In vitro studies have indicated that bivalirudin inhibits both soluble (free) and clot-bound thrombin. Bivalirudin remains active and is not neutralised by products of the platelet release reaction.

In vitro studies have also shown that bivalirudin prolongs the activated partial thromboplastin time (aPTT) thrombin time (TT) and pro-thrombin time (PT) of normal human plasma in a concentration-dependent manner and that bivalirudin does not induce a platelet aggregation response against sera from patients with a history of Heparin-Induced Thrombocytopenia/Thrombosis Syndrome (HIT/HITTS).

In healthy volunteers and patients, bivalirudin exhibits dose- and concentration-dependent anticoagulant activity as evidenced as prolongation of the ACT, aPTT, PT, INR and TT. Intravenous administration of bivalirudin produces measurable anticoagulation within minutes.

Pharmacodynamic effects

The pharmacodynamic effects of bivalirudin may be assessed using measures of anticoagulation including the ACT. The ACT value is positively correlated with the dose and plasma concentration of bivalirudin administered. Data from 366 patients indicates that the ACT is unaffected by concomitant treatment with a GP IIb/IIIa inhibitor.

Clinical efficacy and safety

In clinical studies bivalirudin has been shown to provide adequate anticoagulation during PCI procedures.

The HORIZONS Trial *(Patients with STEMI undergoing primary PCI)*

The HORIZONS trial was a prospective, dual arm, single blind, randomised, multi-centre trial to establish the safety and efficacy of bivalirudin in patients with STEMI undergoing a primary PCI strategy with stent implantation with either a slow release paclitaxel-eluding stent (TAXUS^{TM}) or an otherwise identical uncoated bare metal stent (Express2^{TM}). A total of 3,602 patients were randomised to receive either bivalirudin (1,800 patients) or unfractionated heparin plus a GP IIb/IIIa inhibitor (1,802 patients). All patients received acetylsalicylic acid and clopidogrel with twice as many patients (approximately 64%) receiving a 600mg loading dose of clopidogrel than a 300mg loading dose

of clopidogrel.

Approximately 66% of patients were pre-treated with unfractionated heparin.

The dose of bivalirudin used in HORIZONS was the same as that used in the REPLACE-2 study (0.75 mg/kg bolus followed by a 1.75 mg/kg body weight/hour infusion). A total of 92.9% of patients treated underwent primary PCI as their primary management strategy.

The analysis and results for the HORIZONS trial at 30 days for the overall (ITT) population is shown in Table 2. Results at 1 year were consistent with results at 30 days.

Bleeding definitions and outcomes from the HORIZONS trial are shown in Table 6.

Table 2. **HORIZONS 30-day study results (intent-to-treat population)**

Endpoint	**Bivalirudin (%)**	**Unfractionated heparin + GP IIb/IIIa inhibitor (%)**	**Relative Risk [95% CI]**	**p-value***
	N = 1,800	N = 1,802		
30 day Composite				
MACE[1]	5.4	5.5	0.98 [0.75, 1.29]	0.8901
Major bleeding[2]	5.1	8.8	0.58 [0.45, 0.74]	<0.0001
Ischaemic Components				
All cause death	2.1	3.1	0.66 [0.44, 1.0]	0.0465
Reinfarction	1.9	1.8	1.06 [0.66, 1.72]	0.8003
Ischaemic target vessel revascularisation	2.5	1.9	1.29 [0.83,1.99]	0.2561
Stroke	0.8	0.7	1.17 [0.54, 2.52]	0.6917

*Superiority p-value. [1] Major Adverse Cardiac/Ischaemic Events (MACE) was defined as the occurrence of any of the following; death, reinfarction, stroke or ischaemic target vessel revascularisation. [2]Major bleeding was defined using the ACUITY bleeding scale.

ACUITY Trial *(Patients with unstable angina/non-ST segment elevated myocardial infarction (UA/NSTEMI)*

The ACUITY trial was a prospective, randomised open-label, trial of bivalirudin with or without GP IIb/IIIa inhibitor (Arms B and C respectively) versus unfractionated heparin or enoxaparin with GP IIb/IIIa inhibitor (Arm A) in 13,819 high risk ACS patients.

In Arms B and C of the ACUITY trial, the recommended dose of bivalirudin was an initial post-randomisation intravenous bolus of 0.1 mg/kg followed by a continuous intravenous infusion of 0.25 mg/kg/h during angiography or as clinically warranted.

For patients undergoing PCI, an additional intravenous bolus of 0.5 mg/kg bivalirudin was administered and the rate of intravenous infusion increased to 1.75 mg/kg/h.

In Arm A of the ACUITY trial, UFH or enoxaparin was administered in accordance with the relevant guidelines for the management of ACS in patients with UA and NSTEMI. Patients in Arms A and B were also randomised to receive a GP IIb/IIIa inhibitor either upfront at the time of randomization (prior to angiography) or at the time of PCI. A total of 356 (7.7%) of patients randomised to Arm C also received a GP IIb/IIIa inhibitor.

High risk patient characteristics of the ACUITY population that mandated angiography within 72 hours were balanced across the three treatment arms. Approximately 77% of patients had recurrent ischaemia, approximately 70% had dynamic ECG changes or elevated cardiac biomarkers, approximately 28% had diabetes and approximately 99% of patients underwent angiography within 72 hours.

Following angiographic assessment, patients were triaged to either medical management (33%), PCI (56%) or CABG (11%). Additional anti-platelet therapy utilised in the study included acetylsalicylic acid and clopidogrel.

The primary analysis and results for ACUITY at 30-days and 1 year for the overall (ITT) population and for the patients that received acetylsalicylic acid and clopidogrel as per protocol (pre-angiography or pre-PCI) are shown in Tables 3 and 4.

Table 3. ACUITY trial; 30-day and 1-year risk differences for the composite ischaemic endpoint and its components for the overall population (ITT)

	Overall population (ITT)				
	Arm A UFH/enox +GP IIb/IIIa inhibitor (N=4,603) %	**Arm B bival +GP IIb/IIIa inhibitor (N=4,604) %**	**B – A Risk diff. (95% CI)**	**Arm C bival alone (N=4,612) %**	**C – A Risk diff. (95% CI)**
30-day					
Composite ischaemia	7.3	7.7	0.48 (-0.60, 1.55)	7.8	0.55 (-0.53, 1.63)
Death	1.3	1.5	0.17 (-0.31, 0.66)	1.6	0.26 (-0.23, 0.75)
MI	4.9	5.0	0.04 (-0.84, 0.93)	5.4	0.45 (-0.46, 1.35)
Unplanned revasc.	2.3	2.7	0.39 (-0.24, 1.03)	2.4	0.10 (-0.51, 0.72)
1-year					
Composite ischaemia	15.3	15.9	0.65 (-0.83, 2.13)	16.0	0.71 (-0.77, 2.19)
Death	3.9	3.8	0.04 (-0.83, 0.74)	3.7	-0.18 (-0.96, 0.60)
MI	6.8	7.0	0.19 (-0.84, 1.23)	7.6	0.83 (-0.22, 1.89)
Unplanned revasc.	8.1	8.8	0.78 (-0.36, 1.92)	8.4	0.37 (-0.75, 1.50)

Table 4. ACUITY trial; 30-day and 1-year risk differences for the composite ischaemic endpoint and its components for patients that received acetylsalicylic acid and clopidogrel as per protocol*

	Patients receiving acetylsalicylic acid & clopidogrel as per protocol*				

	Arm A UFH/enox +GP IIb/IIIa inhibitor (N=2,842) %	Arm B bival +GP IIb/IIIa inhibitor (N=2,924) %	B – A Risk diff. (95% CI)	Arm C bival alone (N=2,911) %	C – A Risk diff. (95% CI)
30-day					
Composite ischaemia	7.4	7.4	0.03 (-1.32, 1.38)	7.0	-0.35 (-1.68, 0.99)
Death	1.4	1.4	-0.00 (-0.60, 0.60)	1.2	-0.14 (-0.72, 0.45)
MI	4.8	4.9	0.04 (-1.07, 1.14)	4.7	-0.08 (-1.18, 1.02)
Unplanned revasc.	2.6	2.8	0.23 (-0.61, 1.08)	2.2	-0.41 (-1.20, 0.39)
1-year					
Composite ischaemia	16.1	16.8	0.68 (-1.24, 2.59)	15.8	-0.35 (-2.24, 1.54)
Death	3.7	3.9	0.20 (-0.78, 1.19)	3.3	-0.36 (-1.31, 0.59)
MI	6.7	7.3	0.60 (-0.71, 1.91)	6.8	0.19 (-1.11, 1.48)
Unplanned revasc.	9.4	10.0	0.59 (-0.94, 2.12)	8.9	-0.53 (-2.02, 0.96)

*clopidogrel pre-angiography or pre-PCI

The incidence of both ACUITY-scale and TIMI-scale bleeding events up to day 30 for the intent-to-treat population is presented in Table 6. The incidence of both ACUITY-scale and TIMI-scale bleeding events to day 30 for the per protocol population are presented in Table 7. The advantage of bivalirudin over UFH/enoxaparin plus GP IIb/IIIa inhibitor in terms of bleeding events was only observed in the bivalirudin monotherapy arm.

The REPLACE-2 Trial *(Patients undergoing PCI)*

The 30-day results based on quadruple and triple endpoints from a randomized, double-blind trial of over 6,000 patients undergoing PCI (REPLACE-2) are shown in Table 5. Bleeding definitions and outcomes from the REPLACE-2 trial are shown in Table 6.

Table 5. REPLACE-2 study results: 30-day endpoints (intent-to-treat and per-protocol populations

Endpoint	**Intent-to-treat**		**Per-protocol**	
	bivalirudin (N=2,994) %	**heparin + GP IIb/IIIa inhibitor (N=3,008) %**	**bivalirudin (N=2,902) %**	**heparin + GP IIb/IIIa inhibitor (N=2,882) %**
Quadruple endpoint	9.2	10.0	9.2	10.0
Triple endpoint*	7.6	7.1	7.8	7.1
Components:				
Death	0.2	0.4	0.2	0.4

Myocardial Infarction	7.0	6.2	7.1	6.4
Major bleeding** (based on non-TIMI criteria - see section 4.8)	2.4	4.1	2.2	4.0
Urgent revascularisation	1.2	1.4	1.2	1.3

* excludes major bleeding component. **p<0.001

Table 6. Major bleeding rates in clinical trials of bivalirudin 30 day endpoints for intent-to-treat populations

	Bivalirudin (%)			**Bival + GP IIb/IIIa inhibitor (%)**	**UFH/Enox[1] + GP IIb/IIIa inhibitor (%)**		
	REPLACE-2	ACUITY	HORIZONS	ACUITY	REPLACE-2	ACUITY	HORIZONS
	N = 2,994	N = 4,612	N = 1,800	N = 4,604	N = 3,008	N = 4,603	N = 1,802
Protocol defined major bleeding	2.4	3.0	5.1	5.3	4.1	5.7	8.8
TIMI Major (non-CABG) Bleeding	0.4	0.9	1.8	1.8	0.8	1.9	3.2

[1]Enoxaparin was used as comparator in ACUITY only.

Table 7. ACUITY trial; bleeding events up to day 30 for the population of patients who received acetylsalicylic acid and clopidogrel as per protocol*

	UFH/enox + GP IIb/IIIa inhibitor (N= 2,842) %	**Bival + GP IIb/IIIa inhibitor (N=2,924) %**	**Bival alone (N=2,911) %**
ACUITY scale major bleeding	5.9	5.4	3.1
TIMI scale major bleeding	1.9	1.9	0.8

*clopidogrel pre-angiography or pre-PCI

Bleeding Definitions

REPLACE-2 major bleeding was defined as the occurrence of any of the following: intracranial haemorrhage, retroperitoneal haemorrhage, blood loss leading to a transfusion of at least two units of whole blood or packed red blood cells, or bleeding resulting in a haemoglobin drop of more than 3 g/dl, or a fall in haemoglobin greater than 4 g/dl (or 12% of haematocrit) with no bleeding site identified. **ACUITY major bleeding** was defined as any one of the following: intracranial, retroperitoneal, intraocular, access site haemorrhage requiring radiological or surgical intervention, ≥5 cm diameter haematoma at puncture site, reduction in haemoglobin concentration of ≥4 g/dl without an overt source of bleeding, reduction in haemoglobin concentration of ≥3 g/dl with an overt source of bleeding, re-operation for bleeding, use of any blood product transfusion. **Major bleeding in the HORIZONS study** was also

defined using the ACUITY scale. **TIMI major bleeding** was defined as intracranial bleeding or a decrease in haemoglobin concentration ≥5 g/dl.

Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia-thrombosis syndrome (HIT/HITTS)

Clinical trials in a small number of patients have provided limited information about the use of bivalirudin in patients with HIT/HITTS.

Paediatric population

In clinical study TMC-BIV-07-01, the pharmacodynamic response as measured by ACT was consistent with adult studies. The ACT increased in all patients – from neonates to older children as well as adults-with increasing bivalirudin concentrations. The ACT vs concentration data suggest a trend for a lower concentration response curve for adults as compared to older children (6 years to < 16 years) and younger children (2 years to <6 years), and for older children compared to infants (31 days to <24 months) and neonates (birth to 30 days). Pharmacodynamic models indicated that this effect is due to a higher baseline ACT in neonates and infants than in older children. However, the maximal ACT values for all groups (adults and all paediatric groups) converge at a similar level near an ACT of 400 seconds. The clinical utility of ACT in neonates and children should be considered with caution considering their developmental haematological state.

Thrombotic (9/110, 8.2%) and major bleeding events (2/110, 1.8%) were observed in the study. Other frequently reported adverse events were decreased pedal pulse, catheter site haemorrhage, abnormal pulse, and nausea (8.2%, 7.3%, 6.4% and 5.5%, respectively). Five patients had a post-baseline nadir platelet count of <150,000 cells/mm^3, representing a ≥50% decrease in platelets from baseline. All 5 events were associated with additional cardiac procedures employing heparin anticoagulation (n=3) or with infections (n=2). A population pharmacokinetic/pharmacodynamic analysis, and an Exposure and Adverse Event Assessment Model based on the data from this study determined that in paediatric patients, use of the adult dosing with plasma levels similar to that achieved in adults was associated with lower levels of thrombotic events with no impact on bleeding events (see section 4.2).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of bivalirudin have been evaluated and found to be linear in patients undergoing Percutaneous Coronary Intervention and in patients with ACS.

Absorption

The bioavailability of bivalirudin for intravenous use is complete and immediate. The mean steady-state concentration of bivalirudin following a constant intravenous infusion of 2.5 mg/kg/h is 12.4 µg/ml.

Distribution

Bivalirudin is rapidly distributed between plasma and extracellular fluid. The steady-state volume of distribution is 0.1 l/kg. Bivalirudin does not bind to plasma proteins (other than thrombin) or to red blood cells.

Biotransformation

As a peptide, bivalirudin is expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acid in the body pool. Bivalirudin is metabolized by proteases, including thrombin. The primary metabolite resulting from the cleavage of Arg_3-Pro_4 bond of the N-terminal sequence by thrombin is not active because of the loss of affinity to the catalytic active site of thrombin. About 20% of bivalirudin is excreted unchanged in the urine.

Elimination

The concentration-time profile following intravenous administration is well described by a two-compartment model. Elimination follows a first order process with a terminal half-life of 25 ± 12 minutes in patients with normal renal function. The corresponding clearance is about 3.4 ± 0.5 ml/min/kg.

Hepatic impairment

The pharmacokinetics of bivalirudin have not been studied in patients with hepatic impairment but are not expected to be altered because bivalirudin is not metabolized by liver enzymes such as cytochrome P-450 isozymes.

Renal impairment

The systemic clearance of bivalirudin decreases with glomerular filtration rate (GFR). The clearance of bivalirudin is similar in patients with normal renal function and those with mild renal impairment. Clearance is reduced by approximately 20% in patients with moderate or severe renal impairment, and 80% in dialysis-dependent patients (Table 8).

Table 8. Pharmacokinetic parameters for bivalirudin in patients with normal and impaired renal function

Renal function (GFR)	**Clearance (ml/min/kg)**	**Half-life (minutes)**
Normal renal function (≥ 90ml/min)	3.4	25
Mild renal impairment (60-89 ml/min)	3.4	22
Moderate renal impairment (30-59 ml/min)	2.7	34
Severe renal impairment (10-29 ml/min)	2.8	57
Dialysis dependent patients (off-dialysis)	1.0	3.5 hours

Elderly

Pharmacokinetics have been evaluated in elderly patients as part of a renal pharmacokinetic study. Dose adjustments for this age group should be on the basis of renal function, see section 4.2.

Gender

There are no gender effects in the pharmacokinetics of bivalirudin.

Paediatric population

In a clinical trial of 110 paediatric patients (neonates to <16 years of age) undergoing percutaneous intravascular procedures, the safety, pharmacokinetic and pharmacodynamic profile of bivalirudin was evaluated [TMC-BIV-07-01]. The approved adult weight-based intravenous bolus dose of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/hour was studied and pharmacokinetic/pharmacodynamic analysis found a response similar to that of adults, although weight-normalized clearance (ml/min/kg) of bivalirudin was higher in neonates than in older children and decreased with increasing age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, or toxicity to reproduction.

Toxicity in animals upon repeated or continuous exposure (1 day to 4 weeks at exposure levels of up to 10 times the clinical steady state plasma concentration) was limited to exaggerated pharmacological effects. Comparison of the single and repeated dose studies revealed that toxicity was related primarily to duration of exposure. All the undesirable effects, primary and secondary, resulting from excessive pharmacological activity were reversible. Undesirable effects that resulted from prolonged physiological stress in response to a non-homeostatic state of coagulation were not seen after short exposure comparable to that in clinical use, even at much higher doses.

Bivalirudin is intended for short-term administration and therefore no data on the long-term carcinogenic potential of bivalirudin are available. However, bivalirudin was not mutagenic or clastogenic in standard assays for such effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium hydroxide

6.2 Incompatibilities

The following medicinal products should not be administered in the same intravenous line as bivalirudin since they result in haze formation, micro-particulate formation or gross precipitation; alteplase, amiodarone HCl, amphotericin B, chlorpromazine hydrochloride (HCl), diazepam, prochlorperazine edisylate, reteplase, streptokinase and vancomycin HCl.

The following six medicinal products show dose-concentration incompatibilities with bivalirudin.

Table 9 summarises compatible and incompatible concentrations of these compounds. The medicinal products incompatible with bivalirudin at higher concentrations are: dobutamine hydrochloride, famotidine, haloperidol lactate, labetalol hydrochloride, lorazepam and promethazine HCl.

Table 9. Medicinal products with dose concentration incompatibilities to bivalirudin.

Medicinal products with dose concentration incompatibilities	Compatible concentrations	Incompatible concentrations
Dobutamine HCl	4 mg/ml	12.5 mg/ml
Famotidine	2 mg/ml	10 mg/ml
Haloperidol lactate	0.2 mg/ml	5 mg/ml
Labetalol HCl	2 mg/ml	5 mg/ml
Lorazepam	0.5 mg/ml	2 mg/ml
Promethazine HCl	2 mg/ml	25 mg/ml

6.3 Shelf life

2 years

Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. Store in a refrigerator (2°C-8°C). Do not freeze.

Diluted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and at 2°C-8°C. Do not store above 25°C. Do not freeze.

From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any specific storage condition.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml vials (Type 1 glass) with stopper (butyl rubber) with seal (aluminum), containing 250 mg bivalirudin.

Pack sizes: 1 and 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for preparation

Aseptic procedures should be used for the preparation and administration of bivalirudin.

Add 5 ml sterile water for injections to one vial of bivalirudin and swirl gently until completely dissolved and the solution is clear. 1 ml reconstituted solution contains 50 mg bivalirudin.

Withdraw 5 ml from the vial, and further dilute in a total volume of 50 ml of glucose 5% solution for injection, or sodium chloride 9 mg/ml (0.9%) solution for injection to give a final bivalirudin concentration of 5 mg/ml.

The reconstituted/diluted solution should be inspected visually for particulate matter and discolouration. Solutions containing particulate matter should not be used.

The reconstituted/diluted solution will be a clear colourless solution, without any visible extraneous matter.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1809/024/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st July 2016

10 DATE OF REVISION OF THE TEXT