ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Angiox 250 mg powder for concentrate for solution for injection or 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 or infusion (powder for concentrate).

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Angiox 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.

Angiox 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.

Angiox should be administered with acetylsalicylic acid and clopidogrel.

4.2 Posology and method of administration

Angiox 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 clinically 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 Angiox 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 Angiox 30 minutes after discontinuation of unfractionated heparin given intravenously, or 8 hours after discontinuation of low molecular weight heparin given subcutaneously.

Angiox 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 insufficiency
Angiox 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 Angiox 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 Angiox 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

Angiox is intended for intravenous use.

Angiox 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

Angiox 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

Angiox 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 ($T_{½}$ is 25 ± 12 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 Angiox.

Angiox should be used with caution during beta brachytherapy procedures.

Excipient

Angiox 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 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).

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

Breastfeeding

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

4.7 Effects on ability to drive and use machines

Angiox 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		
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				Cardiac tamponade, Pericardial haemorrhage, Myocardial infarction, Coronary artery thrombosis, Bradycardia, Ventricular tachycardia' Angina pectoris, 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]

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)
Respiratory, thoracic and mediastinal disorders			Epistaxis, Haemoptysis, Pharyngeal haemorrhage	Pulmonary 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)	
Investigations				INR increased[d]	
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 the national reporting system listed in Appendix V.

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

Angiox 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™) or an otherwise identical uncoated bare metal stent (Express2™). 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 Angiox 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 Insufficiency

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 Insufficiency

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 Pre-clinical 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 2% (for pH adjustment)

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

4 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. 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

Do not store above 25°C.

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

6.5 Nature and contents of container

Angiox is supplied as a lyophilised powder in 10 ml single use glass vials (Type 1) closed with a butyl rubber stopper and sealed with a crimped aluminum seal.

Angiox is available in packs of 10 vials.

6.6 Special precautions for disposal and other handling

Instructions for preparation

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

Add 5 ml sterile water for injections to one vial of Angiox and swirl gently until completely dissolved and the solution is clear.

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 to slightly opalescent, colourless to slightly yellow solution.

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

7. MARKETING AUTHORISATION HOLDER

The Medicines Company UK Ltd
115L Milton Park
Abingdon
Oxfordshire
OX14 4SA
UNITED KINGDOM

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/289/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20.09.2004
Date of latest renewal: 23.06.2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the web site of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Hälsa Pharma GmbH, Nikolaus Dürkopp-Str. 4A, 33602 Bielefeld, GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

In order to ensure the correct use of Angiox and to avoid medication errors, the MAH shall ensure that all prescribers who are expected to prescribe/use Angiox are provided with training on dosing and administration. Educational material includes a slide deck presentation, dosing cards as described in the risk minimization measures in the RMP, and a copy of the SmPC. The educational materials will be used in all member states for both initial training and re-education in the event of reports of bolus only dosing without subsequent infusion.

The slide deck will contain the following key information:

- Approved dose in patients undergoing percutaneous coronary intervention (PCI): The licensed and approved dosing regimen of Angiox is an intravenous (IV) bolus injection of 0.75 mg/kg body weight followed immediately by an intravenous infusion at 1.75 mg/kg/hour for at least the duration of the PCI.
- Angiox must be administered as a bolus dose followed immediately by an intravenous infusion, even if a short PCI procedure is planned. Do not use without dilution.

- For patients undergoing PCI, bivalirudin MUST be administered initially as an intravenous bolus followed immediately by an infusion. This dosing regimen is required to achieve and maintain the plasma concentration required for effective ischaemic protection during PCI. Based on the short half-life of bivalirudin (25 minutes), failure to initiate an infusion following the Angiox bolus will result in a plasma concentration that is below the required level within minutes
- In the ImproveR registry bolus dosing (without subsequent infusion) was observed in EU clinical practice. This dosing pattern was associated with increased in-hospital ischaemic events (MACE). The safety and efficacy of a bolus without subsequent infusion dose of ANGIOX has not been evaluated and is not recommended even if a short PCI procedure is planned.
- Angiox is contraindicated in patients with severe renal insufficiency (glomerular filtration rate (GFR) < 30 ml/min) and in dialysis-dependent patients.
- In patients with moderate renal impairment (GFR 30-59 ml/ min) the infusion rate should be reduced to 1.4 mg/kg/h. The bolus dose remains 0.75 mg/kg (or 0.5 mg/kg in patients who proceed to PCI after receiving bivalirudin pre-cath lab (UA/NSTEMI)).

The dosing cards will contain the following key information:

- Angiox must be administered as a bolus dose followed immediately by an intravenous infusion, even if a short PCI procedure is planned.
- Do not use bivalirudin without first diluting it.
- Tabulated information on dosing by body weight of patient.
- Angiox is contraindicated in patients with severe renal insufficiency (glomerular filtration rate (GFR) < 30 ml/min) and in dialysis-dependent patients.
- In patients with moderate renal impairment (GFR 30-59 ml/ min) the infusion rate should be reduced to 1.4 mg/kg/h. The bolus dose remains 0.75 mg/kg; or 0.5 mg/kg in patients who proceed to PCI after receiving bivalirudin pre-cath lab (UA/NSTEMI).
- Brief information on preparation and administration instructions.

The MAH shall agree on the dosing card together with a communication plan, with the National Competent Authority in each Member State prior to distribution in the Member State.

The use of the Angiox dosing card is recommended as a quick reference guide. Healthcare providers are recommended to refer to the Angiox Summary of Product Characteristics for full information on dosing.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (pack of 10 vials)

1. NAME OF THE MEDICINAL PRODUCT

Angiox 250 mg powder for concentrate for solution for injection or infusion
bivalirudin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 250 mg bivalirudin.
After reconstitution 1 ml contains 50 mg bivalirudin.
After dilution 1ml contains 5 mg bivalirudin.

3. LIST OF EXCIPIENTS

Mannitol, sodium hydroxide 2%

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for injection or infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Lyophilised powder: Do not store above 25°C.

Reconstituted solution: Store in a refrigerator (2 – 8°C). Do not freeze.

Diluted solution: Do not store above 25°C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution should be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

The Medicines Company UK Ltd
115L Milton Park
Abingdon
Oxfordshire
OX14 4SA
UNITED KINGDOM

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/289/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Angiox 250 mg powder for concentrate
bivalirudin
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mg

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Angiox 250 mg powder for concentrate for solution for injection or infusion
bivalirudin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. WHAT ANGIOX IS AND WHAT IT IS USED FOR

Angiox contains a substance called bivalirudin which is an antithrombotic medicine. Antithrombotics are medicines which prevent the formation of blood clots (thrombosis).

Angiox is used to treat patients**:**

- with chest pain due to heart disease (acute coronary syndromes - ACS)
- who are having surgery to treat blockages in their blood vessels (angioplasty and/or percutaneous coronary intervention - PCI).

2. WHAT YOU NEED TO KNOW BEFORE YOU USE ANGIOX

Do not use Angiox

- if you are allergic to bivalirudin or any of the other ingredients of this medicine (listed in section 6) or hirudins (other blood thinning medicines).
- if you have, or have recently had, any bleeding from your stomach, intestines, bladder or other organs, for example, if you have noticed abnormal blood in your stools or urine (except from menstrual bleeding).
- if you have, or have had, difficulty with your blood clotting (a low platelet count).
- if you have severe high blood pressure.
- if you have an infection of the heart tissue.
- if you have severe kidney problems or if you need kidney dialysis.

Check with the doctor if you are unsure.

Warnings and precautions

Talk to your doctor before using Angiox.

- if bleeding occurs (if this happens, treatment with Angiox will be stopped). Throughout your treatment, the doctor will check you for any signs of bleeding.

- if you have been treated before with medicines similar to Angiox (e.g. lepirudin).
- before the start of the injection or infusion, the doctor will tell you about the signs of allergic reaction. Such a reaction is uncommon (may affect up to 1 in 100 people).
- if you are having radiation treatment in the vessels that supply blood to the heart (treatment called beta or gamma brachytherapy).

After being treated with Angiox for a cardiac event, you should stay in the hospital for at least 24 hours and you should be monitored for any symptoms or signs similar to the ones that remind you of your cardiac event and resulted in your hospitalisation.

Children and adolescents

- if you are a child (less than 18 years of age), this medicine is not appropriate for you.

Other medicines and Angiox

tell your doctor
- if you are taking, or have recently taken or might take any other medicines.
- If you are taking blood thinners or medicines to prevent blood clots (anticoagulants or antithrombotics e.g. warfarin, dabigatran, apixaban, rivaroxaban, acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor).

these medicines may increase the risk of side effects such as bleeding when given at the same time as Angiox. Your warfarin blood test result (INR test) may be affected by Angiox.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Angiox should not be used during pregnancy, unless clearly necessary. Your doctor will decide whether or not this treatment is appropriate for you. If you are breast-feeding, the doctor will decide whether Angiox should be used.

Driving and using machines

the effects of this medicine are known to be short-term. Angiox is only given when a patient is in hospital. It is, therefore, unlikely to affect your ability to drive or to use machines.

Angiox contains sodium

This medicine contains less than 23 mg of sodium per vial, which means that it is essentially "sodium-free".

3. HOW TO USE ANGIOX

Your treatment with Angiox will be supervised by a doctor. The doctor will decide how much Angiox you receive, and will prepare the medicine.

The dose given depends on your weight and on the kind of treatment you are being given.

Dosage

For patients with acute coronary syndromes (ACS) who are treated medically the recommended **starting dose** is**:**

- 0.1 mg/kg body weight as an intravenous injection, followed by an infusion (drip) into vein of 0.25 mg/kg body weight per hour for up to 72 hours.

If, after this, **you** then need percutaneous coronary intervention (PCI) treatment, the dosage will be increased to:

- 0.5 mg/kg body weight for the intravenous injection, followed by an infusion into vein of 1.75 mg/kg body weight, per hour for the duration of the PCI.

- When this treatment is finished, the infusion may go back to **0.25 mg/kg** body weight per hour for an additional 4 to 12 hours.

If you need to have a coronary artery bypass graft operation, treatment with bivalirudin will either be stopped one hour before the operation or an additional dose of 0.5 mg/kg body weight will be given by injection followed by an infusion of 1.75 mg/kg body weight per hour for the duration of surgery.

For patients starting with percutaneous coronary intervention (PCI) the recommended dose is:

- **0.75 mg/kg** body weight as an intravenous injection, followed immediately by an infusion (drip) into vein of **1.75 mg/kg** body weight, per hour for at least the duration of the PCI. The intravenous infusion may continue at this dose for up to 4 hours after the PCI and for STEMI patients (those with a severe type of heart attack) it should continue at this dose for up to 4 hours. The infusion may be followed by an infusion at a lower dose of 0.25 mg/kg body weight for an additional 4 to 12 hours.

If you have kidney problems, the dose of Angiox may need to be reduced.

In the elderly, if their kidney function is decreased, the dose may need to be reduced.

The doctor will decide for how long you should be treated.

Angiox is for injection, followed by infusion (drip), into a vein (never into a muscle). This is administered and supervised by a doctor experienced in caring for patients with heart disease.

If you receive more of this medicine than you should

Your doctor will decide how to treat you, including stopping the drug and monitoring for signs of ill effects.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.
If you get any of the following, potentially serious, side effects:

- **while you are in hospital: tell the doctor or nurse immediately –**
- **after you've left hospital: contact your doctor directly or go immediately to the Emergency Department of your nearest hospital -**

The most common, (may affect up to 1 in 10 people) serious side effect of treatment with Angiox, is major bleeding which could occur anywhere inside the body (e.g. stomach, digestive system (including vomiting blood or passing blood with the stools), abdomen, lungs, groin, bladder, heart, eye, ear, nose or brain). This may, **rarely**, result in a stroke or be fatal. Swelling or pain in the groin or the arm, back pain, bruising, headache, coughing blood, pink or red urine, sweating, feeling faint or sick or dizzy due to low blood pressure may be signs of internal bleeding. Bleeding is more likely to occur when Angiox is used in combination with other anticoagulant or antithrombotic medicines (see section 2 'Taking other medicines').

- Bleeding and bruising at the puncture site (after PCI treatment) may be painful. Rarely this may require surgery to repair the blood vessel in the groin (fistula, pseudoaneurysm) (may affect up to 1 in 1,000 people). Uncommonly (may affect up to 1 in 100 people) the number of blood platelets may be low which can worsen any bleeding. Gum bleeding (uncommon, may affect up to 1 in 100 people) is usually not serious.

- Allergic reactions,- are uncommon (may affect up to 1 in 100 people) and usually not serious but can become severe under some circumstances, and in rare cases may be fatal due to low blood pressure (shock). They may begin with limited symptoms such as itching, redness of the skin, rash or small bumps on the skin. Occasionally, reactions can be more severe with throat itching, throat tightening, swelling of the eyes, face, tongue or lips, high pitched whistling during inhaling (stridor), difficulty breathing or exhaling (wheezes).

- Thrombosis (blood clot) is an uncommon side effect (may affect up to 1 in 100 people) which may result in serious or fatal complications such as heart attack. Thrombosis includes coronary artery thrombosis (blood clot in the heart arteries or within a stent being felt as a heart attack which can also be fatal) and/or thrombosis in the catheter, both of which are rare (may affect up to 1 in 1,000 people).

If you get any of the following, (potentially less serious), side effects:

- **while you are in hospital: tell the doctor or nurse -**
- **after you've left hospital: first seek advice from your doctor. If you cannot get access to your doctor go immediately to the Emergency Department of your nearest hospital -**

Very common side effects (may affect more than 1 in 10 people):
- Minor bleeding

Common side effects (may affect up to 1 in 10 people):
- Anaemia (a low blood cell count)
- Haematoma (bruising)

Uncommon side effects (may affect up to 1 in 100 people):
- nausea (feeling sick) and/or vomiting (being sick)

Rare side effects (may affect up to 1 in 1000 people)
- INR test (warfarin blood test result) increased (see Section 2, Other medicines and Angiox)
- Angina or chest pain
- Slow heartbeat
- Rapid heartbeat
- Shortness of breath
- Reperfusion injury (no or slow reflow): impaired flow in the heart arteries after they have been reopened

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE ANGIOX

As Angiox is a hospital only medicine, storage of Angiox is the responsibility of healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month.

Lyophilised (freeze-dried) powder: Do not store above 25°C.

Reconstituted solution**:** Store in a refrigerator (2–8°C). Do not freeze.
Diluted solution: Do not store above 25°C. Do not freeze.

The solution should be a clear to slightly opalescent, colourless to slightly yellow solution.
The doctor will check the solution and will discard it, if it contains particles or is discoloured.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Angiox contains

- The active substance is bivalirudin.
- Each vial contains 250 mg bivalirudin.
- After reconstitution (addition of 5 ml water for injections to the vial to dissolve the powder), 1 ml contains 50 mg bivalirudin.
- After dilution (mixing of 5 ml of the reconstituted solution into an infusion bag [total volume of 50 ml] of glucose solution or sodium chloride solution) 1 ml contains 5 mg bivalirudin.

The other ingredients are mannitol and sodium hydroxide 2% (for pH adjustment)

What Angiox looks like and contents of the pack

Angiox is a powder for concentrate for solution for injection or infusion (powder for concentrate).
Angiox is a white to off-white powder in a glass vial.
Angiox is available in cartons containing 10 vials.

Marketing Authorisation Holder and Manufacturer

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Manufacturer

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This leaflet was last revised in:

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Healthcare professionals should refer to the Summary of Product Characteristics for full prescribing information.

Angiox 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.

Angiox 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.

Angiox should be administered with acetylsalicylic acid and clopidogrel.

Instructions for preparation

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

Add 5 ml sterile water for injections to one vial of Angiox and swirl gently until completely dissolved and the solution is clear.

Withdraw 5 ml from the vial, and further dilute in a total volume of 5% 50 ml of glucose 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 to slightly opalescent, colourless to slightly yellow solution.

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

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. See section 6.2 for the summary of 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.

Contraindications

Angiox 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. (*see section 4.3 of SmPC).*

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 clinically 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/h 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.

Renal insufficiency
Angiox 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.

Hepatic impairment
No dose adjustment is needed.
(For full information on posology see section 4.2 of SmPC)

Shelf life

4 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. Do not store above 25°C. Do not freeze.