

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 a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for injection or infusion.

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 aspirin 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 primary PCI

The recommended dose of Angiox 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 may be continued for up to 4 hours post-PCI as clinically warranted. After cessation of the 1.75 mg/kg /h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4 – 12 hours as clinically necessary.

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 Angiox for patients with 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 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 (IV) 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 infusion for the duration of the surgery.

For patients who proceed to CABG surgery on pump, the IV 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).

The safety and efficacy of a bolus only dose of Angiox has not been evaluated and is not recommended even if a short PCI procedure is planned.

The activated clotting time (ACT) may be used to assess bivalirudin activity.

In order to reduce the potential for low ACT values, the reconstituted and diluted product should be thoroughly mixed prior to administration and the bolus dose administered by a rapid intravenous push.

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 infusion dose is properly administered.

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

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.

During PCI, monitoring of clotting time such as the ACT is recommended in patients with renal insufficiency.

The ACT should be checked at 5 minutes post bolus dose. If the 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.

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

Caution should be exercised in the elderly due to age-related decrease in renal function.

Paediatric patients

There is no relevant indication for use of Angiox in children less than 18 years old.

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. Refer to section 5.1 for further information regarding the use of bivalirudin with or without a GP IIb/IIIa inhibitor.

Method of administration

Angiox is intended for intravenous (IV) 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.

Refer to section 6.6 for full instructions regarding the method of administration.

Angiox is administered as a weight based regimen consisting of an initial bolus (by rapid IV push) followed by an IV infusion.

4.3 Contraindications

Angiox is contraindicated in patients with:

- a known hypersensitivity to the active substance or to any of the excipients, 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 ($T_{1/2}$ is 35 to 40 minutes).

Co-administration with platelet inhibitors or anti-coagulants

Combined use of anti-coagulant medicines 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 ($\geq 1/1,000$ to $\leq 1/100$) 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 ($\leq 1/10,000$) 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). 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.

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 medicine, 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

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

4.8 Undesirable effects

In all clinical studies bleeding data were collected separately from adverse drug reactions and are summarised in Table 8 together with the bleeding definitions used for each study.

The HORIZONS Trial (Patients with STEMI undergoing primary PCI)

The following adverse reaction 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 ($p=0.7754$).

Platelets, bleeding and clotting

In the HORIZONS study both major and minor bleeding occurred commonly ($\geq 1/100$ 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 8. 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 aspirin, all but 1 received clopidogrel and 15 also received a GP IIb/IIIa inhibitor.

Table 1. HORIZONS trial; adverse drug reaction data

System organ class	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $\leq 1/100$)	Rare $\geq 1/10,000$ to $\leq 1/1,000$
Blood and the lymphatic system disorders		Anaemia, Thrombocytopenia	
Immune system disorders		Hypersensitivity including anaphylactic reaction and shock, including reports with fatal outcome	
Nervous system disorders		Intracranial haemorrhage	Headache
Cardiac disorders		Angina pectoris, Coronary artery thrombosis	
Vascular disorders	Major haemorrhage at any site, including reports with fatal outcome, Minor haemorrhage	Haematoma, Hypotension	Vascular pseudoaneurysm
Gastrointestinal disorders		Retroperitoneal haemorrhage, Haematemesis, Gastrointestinal haemorrhage, Melaena, Nausea	Oesophageal haemorrhage, Peritoneal haemorrhage, Retroperitoneal haematoma, Vomiting
Respiratory, thoracic and mediastinal disorders		Haemoptysis, Epistaxis, Pulmonary haemorrhage	
Skin and subcutaneous tissue disorders	Echymosis		Rash
Musculoskeletal and connective tissue disorders			Groin pain
Injury, poisoning and procedural complications	Coronary stent thrombosis including reports with fatal outcome, Vessel puncture site haematoma, Vessel	Reperfusion injury (no or slow reflow), Contusion	

System organ class	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $\leq 1/100$)	Rare $\geq 1/10,000$ to $\leq 1/1,000$
	puncture site haemorrhage		
Renal and urinary disorders		Haematuria	

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

The following adverse reaction 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 2.

Platelets, bleeding and clotting

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

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 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 ($\geq 1/10$) and major bleeding occurred commonly ($\geq 1/100$ and $< 1/10$).

Major bleeding rates are shown in Table 8 for the IIT population and Table 10 for the per protocol population (patients receiving clopidogrel and aspirin). 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.

Table 2. ACUITY trial; adverse reaction data

System organ class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $\leq 1/100$)	Rare $\geq 1/10,000$ to $\leq 1/1,000$
Blood and lymphatic system disorders			INR increased, Thrombocytopenia,	

System organ class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $\leq 1/100$)	Rare $\geq 1/10,000$ to $\leq 1/1,000$
			Anaemia.	
Immune system disorders			Hypersensitivity, including anaphylactic reaction and shock, including reports with fatal outcome	
Nervous system disorders			Headache	Intracranial haemorrhage
Ear and labyrinth disorders				Ear haemorrhage
Cardiac disorders				Bradycardia, Pericardial haemorrhage
Vascular disorders	Minor haemorrhage at any site	Major haemorrhage at any site including reports with fatal outcome, Thrombosis including reports with fatal outcome	Hypotension,	Vascular pseudoaneurysm
Respiratory, thoracic and mediastinal disorders			Epistaxis	Pharyngeal haemorrhage, Haemoptysis
Gastrointestinal disorders			Gastrointestinal haemorrhage, Gingival haemorrhage, Nausea, Retroperitoneal haemorrhage, Melaena, Vomiting	Haematemesis
Skin and subcutaneous tissue disorders		Ecchymosis		Urticaria, Rash
Musculoskeletal and connective tissue disorders			Chest pain, Back pain, Groin pain	
Renal and urinary disorders			Haematuria	
General disorders and administration site conditions	Vessel puncture site haemorrhage, Vessel puncture site haematoma < 5 cm		Vessel puncture site haematoma > 5 cm	Injection site reactions

The REPLACE-2 Trial (Patients undergoing PCI)

The following adverse reaction 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 3.

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 is shown in Table 8.

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 ($\geq 1/10$) and major bleeding occurred commonly ($\geq 1/100$ 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 aspirin and clopidogrel, and 10 out of 20 patients also received a GP IIb/IIIa inhibitor. Mortality among these patients was nil.

Table 3. REPLACE-2 trial; adverse reaction data

System organ class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $\leq 1/100$)	Rare $\geq 1/10,000$ to $\leq 1/1,000$
Blood and the lymphatic system disorders			Thrombocytopenia, anaemia	
Immune system disorders			Hypersensitivity, including anaphylactic reaction and shock, including reports with fatal outcome	
Nervous system disorders			Headache	Intracranial haemorrhage
Ear and labyrinth disorders				Ear haemorrhage
Cardiac disorders			Angina pectoris, Pericardial haemorrhage, Ventricular	

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
			tachycardia, Bradycardia	
Vascular disorders	Minor haemorrhage at any site	Major haemorrhage at any site, including reports with fatal outcome, Thrombosis including reports with fatal outcome	Hypotension, Vascular disorder, Vascular anomaly	
Respiratory, thoracic and mediastinal disorders			Epistaxis, Pharyngeal haemorrhage, Dyspnoea, Haemoptysis	
Gastrointestinal disorders			Nausea, Gingival haemorrhage Vomiting, Retroperitoneal haemorrhage, Gastrointestinal haemorrhage	
Skin and subcutaneous tissue disorders			Rash, Urticaria	
Musculoskeletal and connective tissue disorders			Back pain	
Renal and urinary disorders			Haematuria	
General disorders and administration site conditions			Vessel puncture site haemorrhage, Injection site pain, Chest pain, Injection site haemorrhage.	

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: Direct thrombin inhibitors, ATC code: B01AE06.

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, Arg₃-Pro₄, 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.

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.

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 paclitaxal-eluting 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 aspirin 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 4. Results at 1 year were consistent with results at 30 days.

Bleeding definitions and outcomes from the HORIZONS trial are shown in Table 8.

Table 4. 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 AUCITY 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 IV bolus of 0.1 mg/kg followed by a continuous IV infusion of 0.25 mg/kg/h during angiography or as clinically warranted.

For patients undergoing PCI, an additional IV bolus of 0.5 mg/kg bivalirudin was administered and the rate of IV 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 aspirin 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 aspirin and clopidogrel as per protocol (pre-angiography or pre-PCI) are shown in Tables 5 and 6.

Table 5. 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 6. ACUITY trial; 30-day and 1-year risk differences for the composite ischaemic endpoint and its components for patients that received aspirin and clopidogrel as per protocol*

	Patients receiving aspirin & 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 8. The incidence of both ACUITY-scale and TIMI-scale bleeding events to day 30 for the per protocol population are presented in Table 9. 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 7. Bleeding definitions and outcomes from the REPLACE-2 trial are shown in Table 8.

Table 7. 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 8. 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		REPLACE -2	ACUITY	HORIZONS
	N = 2,994	N = 4,612	N = 1,800		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

¹Enoxaparin was used as comparator in ACUITY only.

Table 9. ACUITY trial; bleeding events up to day 30 for the population of patients who received aspirin 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.

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 μ g/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 Arg₃-Pro₄ 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 10).

Table 10. 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 (≥ 90 ml/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

In patients with renal insufficiency, coagulation parameters such as the ACT should be monitored during Angiox therapy.

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.

Weight: Bivalirudin dose is body weight adjusted in mg/kg.

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 solution (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 HCl, diazepam, prochlorperazine edisylate, reteplase, streptokinase and vancomycin HCl.

The following six drugs show dose-concentration incompatibilities with bivalirudin. Table 11 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 11. Drugs with dose concentration incompatibilities to bivalirudin.

Drugs 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.

Diluted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

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

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.

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 2 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 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 solution for injection 5%, 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/1/04/289/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20.09.2004/20.09.2009

10. DATE OF REVISION OF THE TEXT

11/2009

Detailed information on this product is available on the web site of the European Medicines Agency (EMA) <http://www.emea.europa.eu>

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Hälsa Pharma GmbH, Immermannstraße 9, 33619 Bielefeld, GERMANY

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 8 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (pack of 2 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
2 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

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/1/04/289/002

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

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 {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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 for solution for injection or infusion
bivalirudin
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

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 and infusion bivalirudin

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. What Angiox is and what it is used for
2. Before you are given Angiox
3. How Angiox is used
4. Possible side effects
5. How to store Angiox
6. Further information

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. BEFORE YOU ARE GIVEN ANGIOX

Do not use Angiox

- if you are allergic (hypersensitive) to bivalirudin or any of the other ingredients of Angiox (See section 6 for a list of these) or hirudins.
- 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.

Take special care with 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 rare (affects 1 to 10 users in 10,000).
- if you are having radiation treatment in the vessels that supply blood to the heart (treatment called beta or gamma brachytherapy).
- if you are a child (less than 18 years of age), as this medicine is not appropriate for you.

Taking other medicines

Please tell your doctor

- if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.
- If you are taking blood thinners (anticoagulants e.g. warfarin) or medicines to prevent blood clots (antithrombotics).

Because these medicines may increase the risk of side effects such as bleeding when given at the same time as Angiox.

Pregnancy and breast-feeding

You **must** tell the doctor if:

- you are pregnant or think you may be pregnant
- you are planning to become pregnant
- you are breast-feeding.

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

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

3. HOW ANGIOX IS USED

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

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.

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) the recommended starting dose is:

- **0.1 mg/kg** body weight as an injection, followed by an infusion (drip) of **0.25 mg/kg** body weight per hour.

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 injection, followed by an infusion of **1.75 mg/kg** body weight, per hour.
- When this treatment is finished, the infusion may go back to **0.25 mg/kg** body weight, per hour.

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

- **0.75 mg/kg** body weight as an injection, followed immediately by an infusion of **1.75 mg/kg** body weight, per hour. (The infusion may continue for up to 4 hours).

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

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

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 product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Angiox can cause side effects, although not everybody gets them. These side effects may occur with certain frequencies, which are defined as follows:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

If side effects occur, they may need medical attention.

The most common, important side effect of treatment with Angiox, is bleeding which could occur anywhere in the body. This can become serious, and may, **rarely**, be fatal. Bleeding is more likely to occur when Angiox is used in combination with other anticoagulant or antithrombotic medicines (see section 2 'Taking other medicines').

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: go immediately to the Emergency Department of your nearest hospital -**
- **Bleeding** – a **very common** side effect. This could result in complications such as anaemia (a low blood cell count) or haematoma (bruising).
- **Allergic reactions**, such as hives (nettle rash), itching all over your body, tightness of the chest. These are **uncommon** reactions that may be serious or even fatal.
- **Thrombosis** (blood clots) a **common** side effect which may result in serious or fatal complications such as heart attack.

- **Bleeding and bruising at the puncture site** (after PCI treatment) which may be painful. These side effects are **common**.

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: go immediately to the Emergency Department of your nearest hospital -**

Uncommon side effects:

- **severe** bruising (which may be due to a reduction in the number of platelets in your blood. This may prevent your blood from clotting as well as it should)
- headache
- changes in blood pressure
- changes in the rate of your heart beat
- nausea (feeling sick) and/or vomiting (being sick)
- back pain
- chest pain
- shortness of breath
- rash

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE ANGIOX

Keep out of the reach and sight of children.

Angiox is not to be used 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. FURTHER INFORMATION

What Angiox contains

- The active substance is bivalirudin.
 - Each vial contains 250 mg bivalirudin.
 - After reconstitution 1ml contains 50 mg bivalirudin.
 - After dilution 1ml contains 5 mg bivalirudin.
- The other ingredients are mannitol and sodium hydroxide (for pH adjustment)

What Angiox looks like and contents of the pack

Angiox is a white to off-white powder in a glass vial.

Angiox is available in cartons containing 2 and 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

The Medicines Company UK Limited
115L Milton Park
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OX14 4SA
UNITED KINGDOM

Manufacturer

Hälsa Pharma GmbH
Immermannstraße 9
33619 Bielefeld
GERMANY

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site:
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