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.