

ANGIOMAX[®]

NAME OF THE DRUG

Angiomax[®] (bivalirudin) Powder for Injection 250 mg and 100 mg (lyophilised product).

PRESENTATION

Angiomax[®] is supplied in single-use vials as a white lyophilised cake, which is sterile. Each vial contains either: 250 mg bivalirudin present as bivalirudin trifluoroacetate (salt) hydrate and 125 mg mannitol; or 100 mg bivalirudin present as bivalirudin trifluoroacetate (salt) hydrate and 50 mg mannitol. Both presentations also contain sodium hydroxide.

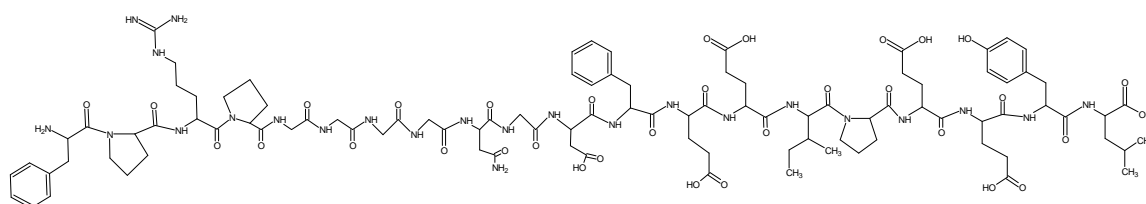
When reconstituted with Water for Injections the product yields a clear to opalescent, colourless to slightly yellow solution, pH 5 to 6.

USES

Description

Angiomax[®] (bivalirudin) is a specific and reversible direct thrombin inhibitor. Bivalirudin is a synthetic, 20 amino acid residue peptide. Its chemical name is D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine (Figure 1). Its molecular weight is 2180 daltons. The substance isolated from the synthesis and used in the manufacture of Angiomax[®] is bivalirudin trifluoroacetate (salt) hydrate.

Figure 1. Structural formula for bivalirudin



ACTIONS

Pharmacology

Angiomax[®] directly inhibits thrombin by binding both to the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin.

Thrombin is a serine proteinase that plays a central role in the thrombotic process. It acts to cleave fibrinogen into fibrin monomers and activates Factor

XIII to Factor XIIIa, allowing fibrin to develop a covalently cross-linked framework which stabilises the thrombus. Thrombin also activates Factors V and VIII, promoting further thrombin generation, and activates platelets, stimulating aggregation and granule release.

The binding of Angiomax[®] to thrombin is reversible.

Pharmacokinetics

After intravenous injection (IV), bivalirudin is almost instantaneously distributed to a volume (V) approximately equal to the sum of plasma and interstitial fluid. Bivalirudin is metabolised predominantly by plasma proteases and exhibits rapid plasma clearance. In normal subjects and patients, bivalirudin has a mean half-life (T_{1/2}) around 25 minutes. Bivalirudin is rapidly cleared from plasma by a combination of renal mechanisms and proteolytic cleavage. Clearance is not dose-dependent. Bivalirudin is readily soluble in water and freely filtered at the glomerulus. Bivalirudin fragments are inactive *in vivo*.

Total plasma clearance of bivalirudin is similar for patients with normal renal function (≥ 90 GFR mL/min) and with mild renal impairment (60-89 GFR mL/min). In patients with moderate (30-59 GFR mL/min) and severe (10-29 GFR mL/min) renal impairment, plasma clearance of bivalirudin is reduced by approximately 20%. In dialysis-dependent patients, clearance is reduced by approximately 80%. For patients with severe renal impairment and for patients on dialysis, monitoring of activated clotting time (ACT) may be advisable (see Table 1, below, and **DOSAGE AND ADMINISTRATION, Renal Impairment**).

Table 1 summarises the main pharmacokinetic parameters of bivalirudin for patients with normal and impaired renal function.

As Angiomax[®] is excreted by the kidneys, each individual's renal function should be considered prior to administration. For patients with renal insufficiency not undergoing PCI, the ACS bolus dose and infusion dose should not be adjusted. For patients with renal insufficiency undergoing PCI, the dose of Angiomax[®] may need to be reduced, and the anticoagulation status (ACT levels) monitored. See **DOSAGE AND ADMINISTRATION (Renal impairment)**.

Table 1. Pharmacokinetic parameters and proposed dose adjustment for patients with renal impairment undergoing PCI.

Renal function (GFR mL/min)	Clearance (mL/min/kg)	Half-life (minutes)	% reduction in infusion dose
Normal (≥ 90)	3.4	25	0
Mild impairment (60-89)	3.4	22	0
Moderate (30-59)	2.7	34	0

Severe (10-29)	2.8	57	20
Dialysis-dependent (off dialysis)	1.0	310	80

Glomerular filtration may contribute to clearance of intact bivalirudin peptide.

Bivalirudin does not bind to plasma proteins (other than thrombin) or to red blood cells.

Bivalirudin is haemodialysable.

Pharmacodynamics

Bivalirudin inhibits the action of thrombin by bivalent binding to the anion binding site and the active site of thrombin. It is slowly cleaved at the Arg³-Pro⁴ bond, which results in recovery of thrombin catalytic site action.

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 prothrombin 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 history of Heparin-Induced Thrombocytopenia/Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HIT/HITTS).

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

In clinical studies Angiomax[®] has been shown to provide adequate anticoagulation during the percutaneous coronary intervention (PCI) procedure, including studies in patients with, or at risk of, HIT/HITTS.

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

Intravenous administration of Angiomax[®] produces an immediate anticoagulant effect. Coagulation times return to sub-therapeutic values within approximately two hours following cessation of Angiomax[®] administration.

CLINICAL TRIALS

Acute Coronary Syndrome (ACS) [unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI)]**ACUITY trial**

Angiomax[®] was evaluated in a randomised, open-label study (ACUITY), intended to determine the non-inferiority and/or superiority of Angiomax[®] with or without GP IIb/IIIa inhibitor to unfractionated heparin or enoxaparin heparin with GP IIb/IIIa inhibitor in patients with moderate or high-risk acute coronary syndromes (ACS) (unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI)). The study's primary endpoints consisted of a net clinical outcome of death, myocardial infarction (MI), unplanned revascularisation for ischaemia, or major bleeding (ACUITY scale); a composite ischaemic endpoint of death, MI or unplanned revascularisation for ischaemia; and major bleeding (ACUITY scale) at 30 days.

Patients with a calculated serum creatinine clearance < 30 mL/min, determined using the Cockcroft and Gault formula, were excluded from the ACUITY study.

All patients received aspirin prior to treatment. Patients were randomised to receive either Angiomax[®] monotherapy (n=4612), Angiomax[®] plus planned GP IIb/IIIa inhibitor (n=4604), or unfractionated heparin or enoxaparinheparin plus planned GP IIb/IIIa inhibitor (n=4603). Provisional GP IIb/IIIa inhibitor could be administered to patients in the Angiomax[®] monotherapy group for procedural or angiographic complications at any time during the PCI. In the Angiomax[®] monotherapy group, 6.5% of PCI patients received both Angiomax[®] and a GP IIb/IIIa inhibitor, and 93.5% received Angiomax[®] alone. In the Angiomax[®] plus planned GP IIb/IIIa inhibitor group, 95.7% of PCI patients received both Angiomax[®] and a GP IIb/IIIa inhibitor, and 4.3% of patients received Angiomax[®] alone. In the unfractionated heparin or enoxaparinheparin plus planned GP IIb/IIIa inhibitor group, 95.6% of all PCI patients received a GP IIb/IIIa inhibitor, and 4.4% of patients received unfractionated heparin or enoxaparinheparin alone.

This study was powered to show non-inferiority and/or superiority. Analyses to determine superiority was performed only if non-inferiority was established. The primary analysis and results for ACUITY at day 30 and at 1 year for the overall (ITT) population and for those patients who received both aspirin and clopidogrel as per the protocol (pre-angiography or pre-PCI) are shown in Tables 2 and 3.

In the ITT population (Table 2), at 30 days, Use of Angiomax[®] alone was superior to heparin or enoxaparin plus planned GP IIb/IIIa inhibitor with regards to major bleeding (ACUITY scale) (3.0% vs 5.7%, $P_{\text{sup}} < 0.0001$) and for the net clinical outcome endpoint (10.1% vs 11.7%, $P_{\text{sup}} < 0.0148$). Use of Angiomax[®] alone was non-inferior to unfractionated heparin or enoxaparinheparin plus planned GP IIb/IIIa inhibitor for the composite ischaemic endpoint (7.8% vs 7.3%, $P_{\text{inf}} = 0.0199$). Angiomax[®] plus planned GP IIb/IIIa inhibitor was non-inferior to unfractionated heparin or enoxaparinheparin plus planned GP IIb/IIIa inhibitor for net clinical outcome

endpoint (11.8% vs 11.7%, $P_{\text{inf}} < 0.0001$), the composite ischaemic endpoint (7.7% vs 7.3%, $P_{\text{inf}} = 0.0074$) and for major bleeding (5.3% vs 5.7%, $P_{\text{inf}} < 0.0001$). At 12 months follow-up, Angiomax[®] either with or without GP IIb/IIIa inhibitors (15.9%) was non-inferior to unfractionated heparin or enoxaparin plus GP IIb/IIIa inhibitors (15.3%) for the composite ischaemic endpoint of death, MI, or unplanned revascularisation.

The advantage of bivalirudin over unfractionated heparin or enoxaparin plus GPIIb/IIIa inhibitor in terms of bleeding events was only observed in the bivalirudin monotherapy arm.

Table 2: Net clinical and component efficacy outcomes at 30-days and 1 year - ITT population

Arm A Heparin ^a + Planned GP IIb/IIIa (N = 4603)	Arm B Bivalirudin + Planned GP IIb/IIIa (N = 4604)	Arm C Bivalirudin (N = 4612)	Risk ratios Arm C vs Arm A	Arm C vs Arm A (Bivalirudin alone vs Heparin + Planned GP IIb/IIIa)		
				95% CI	P-value	
	(%)	(%)	(%)			
30 day						
Net clinical outcomes ^b	11.7	11.8	10.1	0.8645	(0.7689, 0.9719)	<0.001 ^e 0.0148 ^f
Composite ischaemic endpoint ^c	7.3	7.7	7.8	1.0757	(0.9322, 1.2414)	0.0199 ^e 0.3176 ^f
Death	1.3	1.5	1.6	1.1912	(0.8521, 1.6652)	0.3059 ^f
Myocardial infarction	4.9	5.0	5.4	1.0904	(0.9150, 1.2994)	0.3335 ^f
Unplanned revascularisation	2.3	2.7	2.4	1.0456	(0.8028, 1.3619)	0.7410 ^f
Major bleeding ^d	5.7	5.3	3.0	0.5295	(0.4328, 0.6478)	<0.001 ^f
1 year						
Composite ischaemic endpoint ^c	15.3	15.9	16.0	1.0464	(0.9516, 1.1507)	0.3495 ^f
Death	3.9	3.8	3.7	0.9532	(0.7756, 1.1715)	0.6486 ^f
Myocardial infarction	6.8	7.0	7.6	1.1228	(0.9694, 1.3005)	0.1223 ^f
Unplanned revascularisation	8.1	8.8	8.4	1.0465	(0.9132, 1.1992)	0.5135 ^f

Key: a: unfractionated heparin or enoxaparin

b: Composite incidence of death, MI, unplanned revascularisation or major bleeding

c: Composite incidence of death, MI and unplanned revascularisation

d: Major (non-CABG) bleeding was defined by the protocol as any of the following: intracranial haemorrhage, retroperitoneal haemorrhage, intraocular haemorrhage, access site haemorrhage requiring radiological or surgical intervention, ≥ 5 cm haematoma at puncture site, a fall in HgB > 4 g/dL without an overt source of bleeding, a fall in HgB > 3 g/dL with an overt source of bleeding, re-operation for bleeding, use of any blood product transfusion. The TIMI major scale includes only intracranial bleeds or a fall in HgB > 5 g/dL and hence the ACUITY scale is a more sensitive measure of bleeding than the TIMI scale.

e: One sided (non-inferiority) test with significance level 0.025

f: Two-sided (superiority) test with significance level 0.05. Analyses to determine superiority was performed only if non-inferiority was established.

For patients that received aspirin and clopidogrel as per protocol (Table 3), at 30 days, use of Angiomax[®] alone was superior to heparins plus planned GP IIb/IIIa inhibitor with regards to major bleeding (ACUITY scale) (3.1% vs 5.9%, $P_{\text{sup}} < 0.0001$) and for the net clinical endpoint (9.5% vs 11.8%, $P_{\text{sup}} = 0.0052$).

Table 3: 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^a

Endpoint	Arm A Heparin ^a + Planned GP IIb/IIIa (N = 4603)	Arm B Bivalirudin + Planned GP IIb/IIIa (N = 4604)	Arm C Bivalirudin (N = 4612)	Risk ratios Arm C vs Arm A	Arm C vs Arm A (Bivalirudin alone vs Heparin + Planned GP IIb/IIIa)	
					95% CI	P-value
	(%)	(%)	(%)			
30 day						
Net clinical outcomes ^c	11.8	11.4	9.5	0.8073	(0.69, 0.94)	<0.0001 ^f 0.0053 ^g
Composite ischaemic endpoint ^d	7.4	7.4	7.0	0.9531	(0.7918, 1.1472)	0.6111 ^g
Death	1.4	1.4	1.2	0.9012	(0.5746, 1.4134)	0.6505 ^g
Myocardial infarction	4.8	4.9	4.7	0.9834	(0.7808, 1.2386)	0.8871 ^g
Unplanned revascularisation	2.6	2.8	2.2	0.8444	(0.6067, 1.1751)	0.3158 ^g
Major bleeding ^e	5.9	5.4	3.1	0.5261	(0.41, 0.68)	<0.0001 ^g
1 year						
Composite ischaemic endpoint ^d	16.1	16.8	15.8	0.9784	(0.8689, 1.1017)	0.7187 ^g
Death	3.7	3.9	3.3	0.9019	(0.6877, 1.1828)	0.4555 ^g
Myocardial infarction	6.7	7.3	6.8	1.0280	(0.8482, 1.2458)	0.7787 ^g
Unplanned revascularisation	9.4	10.0	8.9	0.9435	(0.8018, 1.1103)	0.4838 ^g

Key: a: Clopidogrel pre-angiography or pre-PCI

b: Unfractionated heparin or enoxaparin

c: Composite incidence of death, MI, unplanned revascularisation or major bleeding

d: Composite incidence of death, MI and unplanned revascularisation

e: Major (non-CABG) bleeding was defined by the protocol as any of the following: intracranial haemorrhage, retroperitoneal haemorrhage, intraocular haemorrhage, access site haemorrhage requiring radiological or surgical intervention, ≥ 5 cm haematoma at puncture site, a fall in HgB > 4 g/dL without an overt source of bleeding, a fall in HgB > 3 g/dL with an overt source of bleeding, re-operation for bleeding, use of any blood product transfusion. The TIMI major scale includes only intracranial bleeds or a fall in HgB > 5 g/dL and hence the ACUITY scale is a more sensitive measure of bleeding than the TIMI scale.

f: One sided (non-inferiority) test with significance level 0.025

g: Two-sided (superiority) test with significance level 0.05. Analyses to determine superiority was performed only if non-inferiority was established.

Description of the patient population

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 coronary artery bypass graft (CABG) (11%). Additional anti-platelet therapy utilised in the study included aspirin and clopidogrel.

Overall, 64% of patients in either treatment group were administered unfractionated heparin or enoxaparin in the period up to 7 days prior to entry into hospital and randomisation (63.9% Angiomax[®] alone vs 63.1% Angiomax[®] +plus GP IIb/IIIa vs 65.4% unfractionated heparin or enoxaparinheparin +plus GP IIb/IIIa). Pre-treatment with aspirin occurred in 96.0% of patients in either treatment group in the ITT population. The majority of patients received pre-treatment with a thienopyridine derivative to inhibit ADP-induced platelet aggregation, with clopidogrel or ticlopidine administered to 64.2% of patients in the Angiomax[®] monotherapy arm, 64.7% of patients in the Angiomax[®] +plus GP IIb/IIIa arm, and 62.8% of patients in the unfractionated heparin or enoxaparinheparin +plus GP IIb/IIIa arm. Administration of clopidogrel was widespread, with only 0.7% of patients in either treatment arm receiving ticlopidine.

For patients randomised to the Angiomax[®] arms, an IV bolus of Angiomax[®] of 0.1 mg/kg was administered followed by an IV infusion of Angiomax[®] at 0.25 mg/kg/hour. For patients being medically managed, the dosage of 0.25 mg/kg/hour was continued at the clinician's discretion. These infusions continued for a mean of 16.9 hours, with 722 patients (21%) receiving Angiomax for over 48 hours and 281 (8%) for over 72 hours with a maximum exposure of 167 hours. For patients who underwent PCI, an additional bolus of 0.50 mg/kg was administered and the infusion rate increased to 1.75 mg/kg/hour for the duration of the procedure (mean 3.2 ± 13.1 hours, range 0.02, 166.8 hours). Post-procedural infusions of Angiomax[®] (0.25 mg/kg/hour) were continued in 6.4% of patients for a mean of $9.9 + 15.1$ hours, range of 0.02, 163.3 hours, at the clinician's discretion.

For patients randomised to the unfractionated heparin plus planned GP IIb/IIIa inhibitor arm, an initial IV bolus injection of 60 U/kg unfractionated heparin was administered, followed by a 12 U/kg/hour infusion for the duration of the procedure.

For patients randomised to the enoxaparin plus planned GP IIb/IIIa inhibitor arm, an initial subcutaneous (SC) dose of 1.0 mg/kg was administered every 12 hours until angiography. If the previous SC dose was less than 8 hours before the PCI, then no further enoxaparin was necessary. If the previous SC dose

was administered 8 hours or more before PCI, an additional 0.3 mg/kg IV bolus was administered before PCI.

Percutaneous Coronary Intervention (PCI)

REPLACE-2 trial

Angiomax[®] was evaluated in a randomised, double-blind study (REPLACE-2), intended to determine non-inferiority of Angiomax[®] plus *provisional* GP IIb/IIIa inhibitors to heparin plus *planned* GP IIb/IIIa inhibitors during elective or urgent PCI. The study's primary endpoint consisted of a quadruple composite measure of death, MI, urgent revascularisation, or major haemorrhage at 30 days. Secondary endpoints included a triple composite measure of death, MI, or urgent revascularisation at 30 days.

All patients received aspirin prior to PCI. Provisional GP IIb/IIIa inhibitor could be administered for procedural or angiographic complications at any time during the PCI using a blinded bolus plus infusion. Patients in the Angiomax[®] arm (n=2994) could receive either eptifibatide or abciximab in addition to Angiomax[®]. Patients in the heparin plus planned GP IIb/IIIa inhibitor group (n=3008) could receive placebo. In the Angiomax[®] group, 7.2% of patients received both Angiomax[®] and a GP IIb/IIIa inhibitor, and 92.8% received Angiomax[®] alone. In the heparin plus planned GP IIb/IIIa inhibitor group, in which all patients received the combination of heparin and either eptifibatide or abciximab, 5.2% of patients received placebo.

This study was powered to show non-inferiority. There was no significant difference between the 2 groups (bivalirudin vs heparin respectively) for either the primary (quadruple composite: 9.2% vs 10.0%, $P = 0.32$) or secondary (triple composite: 7.6% vs 7.1%, $P = 0.40$) endpoints. The study outcomes for the primary composite (quadruple) endpoint are shown in Table 4.

Table 4: Quadruple composite and component efficacy outcomes —ITT population

Endpoint	Heparin + Planned GP IIb/IIIa (N = 3008)	Bivalirudin + Provisional GP IIb/IIIa (N = 2994)	Odds Ratio	95% CI	P-value
	(%)	(%)			
Quadruple endpoint	10.0	9.2	0.917	(0.772, 1.089)	0.324
Triple endpoint	7.1	7.6	1.088	(0.895, 1.322)	0.396
Death	0.4	0.2	0.585	(0.230, 1.488)	0.255
Myocardial infarction	6.2	7.0	1.119	(0.912, 1.374)	0.230
Urgent revascularisation	1.4	1.2	0.836	(0.532, 1.313)	0.435
Major bleeding ^a	4.1	2.4	0.570	(0.424, 0.767)	<0.001

Key: a: Major bleeding was defined by the protocol as any of the following: transfusion of whole blood or PRBC ≥ 2 units, intracranial haemorrhage, retroperitoneal haemorrhage, a fall in HgB $> 4\text{g/dL}$ (or 12% of HCT) with no bleeding site identified despite attempts to do so, spontaneous or non-spontaneous blood loss associated with a HgB drop $> 3\text{g/dL}$ (or 10% of HCT).

At 12 months follow-up, mortality was 1.9% amongst patients randomised to Angiomax[®] plus provisional glycoprotein (GP) IIb/IIIa inhibitors and 2.5% amongst patients randomised to heparin plus planned GP IIb/IIIa inhibitors.

Description of patient population

Less than 15% of patients in either treatment group were administered heparin up to 48 hours prior to PCI: 12.3% vs 10.9% in the heparin plus planned GP IIb/IIIa inhibitor and Angiomax[®] groups, respectively. Similarly, less than 15% of patients in either treatment group were administered low molecular weight heparin up to 48 hours prior to PCI: 10.4% vs 9.6% in the low molecular weight heparin plus planned GP IIb/IIIa inhibitor and Angiomax[®] groups, respectively. Pre-treatment with aspirin occurred in 99.0% of patients in either treatment group in the ITT population. The majority of patients received pre-treatment with a thienopyridine derivative to inhibit ADP-induced platelet aggregation, with clopidogrel or ticlopidine administered to 85.4% and 86.7% of patients in the heparin plus planned GP IIb/IIIa inhibitor and Angiomax[®] groups, respectively. Administration of clopidogrel was widespread, with only 1.8% of patients in the heparin plus planned GP IIb/IIIa inhibitor group and 1.7% in the Angiomax[®] group receiving ticlopidine.

For patients randomised to the Angiomax[®] arm, an IV bolus of Angiomax[®] of 0.75 mg/kg was administered prior to device activation (first balloon inflation). Immediately following the IV bolus, an IV infusion of Angiomax[®] at 1.75 mg/kg/hour was commenced and continued for the duration of the PCI procedure. Post-procedural continuation of the Angiomax[®] infusion was for up to 4 hours as required. Patients also received a placebo to match GP IIb/IIIa inhibitor boluses and placebo infusion (saline) for 12 or 18 hours. Provisional use of GP IIb/IIIa inhibitor was considered necessary in 7.2% of patients in the Angiomax[®] treatment arm.

For patients randomised to the heparin plus planned GP IIb/IIIa inhibitor arm, an initial IV bolus injection of weight-adjusted heparin of 65 U/kg (up to 7000 U) was administered prior to device activation (first balloon inflation) followed by an infusion of saline for the duration of the procedure. Post-procedural continuation of the saline infusion was for up to 4 hours as required. A GP IIb/IIIa inhibitor bolus was administered and the infusion initiated prior to PCI (total infusion duration 12 hours for abciximab or 18 hours for eptifibatide). Provisional use of GP IIb/IIIa inhibitor (placebo) was considered necessary in 5.2% of patients in the heparin plus planned GP IIb/IIIa inhibitor treatment arm.

Heparin-Induced Thrombocytopenia/Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HIT/HITTS)

In *in vitro* studies, Angiomax[®] exhibited no platelet aggregation response against sera from patients with a history of HIT/HITTS.

AT-BAT study

The number of HIT/HITTS patients treated is inadequate to reliably assess efficacy and safety in these patients undergoing PCI. Angiomax[®] was administered to a small number of patients with a history of HIT/HITTS or active HIT/HITTS in an uncontrolled, open-label study. Angiomax[®] appeared to provide adequate anticoagulation in these patients. The mean ACT during the PCI in patients with, or at risk of HIT/HITTS was 337 seconds. These results are consistent with those reported for Angiomax[®] in patients who do not have HIT/HITTS and who undergo PCI.

INDICATION

Angiomax[®] is indicated for use as an anticoagulant:

- in the treatment of patients with moderate to high risk acute coronary syndromes (ACS) (unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) who are undergoing early invasive management, and
- in patients undergoing percutaneous coronary intervention (PCI).

Angiomax[®] is intended for use with aspirin.

A P2Y₁₂ antagonist (eg clopidogrel or ticlopidine) may be used in addition to aspirin.

CONTRAINDICATIONS

Angiomax[®] is contraindicated in patients with:

- active bleeding or increased risk of bleeding because of haemostasis disorders and/or irreversible coagulation disorders,
- severe uncontrolled hypertension and subacute bacterial endocarditis,
- hypersensitivity to Angiomax[®] or its components.

WARNINGS AND PRECAUTIONS

Angiomax[®] is not intended for intramuscular administration. There is no known antidote to Angiomax[®].

Haemorrhage

Although most bleeding associated with the use of Angiomax[®] occurs at the site of arterial puncture, haemorrhage can occur at any site. An unexplained fall in blood pressure or hematocrit, or any unexplained symptom, should lead to serious consideration of a haemorrhagic event and cessation of Angiomax[®] administration.

Angiomax[®] should be used with caution in patients with disease states associated with an increased risk of bleeding.

Renal insufficiency

Clearance of Angiomax[®] is reduced in patients with renal insufficiency. For patients with severe renal impairment and for patients on dialysis, monitoring of ACT may be advisable (see **Pharmacokinetics and DOSAGE AND ADMINISTRATION**). Close, active clinical monitoring of the patient should also be considered.

There is no clinical trial evidence regarding the safety and efficacy of Angiomax[®] in patients with creatinine clearance < 30 mL/min. The use of Angiomax[®] in these patients should occur only after careful consideration of the risks vs benefits.

Gamma brachytherapy

Intraprocedural thrombus formation has been observed during gamma brachytherapy procedures with Angiomax[®]. Angiomax[®] is therefore not recommended for use during gamma brachytherapy.

Carcinogenicity, mutagenicity and impairment of fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of Angiomax[®].

In vitro, bivalirudin displayed no genotoxic potential in the bacterial cell reverse mutation assay (Ames test), the Chinese hamster ovary cell forward gene mutation test (CHO/HGPRT), the human lymphocyte chromosomal aberration assay, and the rat hepatocyte unscheduled DNA synthesis (UDS) assay. Bivalirudin displayed no genotoxic potential in the *in vivo* rat micronucleus assay.

Fertility and general reproductive performance in rats were unaffected by subcutaneous doses of bivalirudin up to 150 mg/kg/day starting 2 weeks before mating until late gestation (gestation day 17), but the number of corpora lutea and implantations was decreased at 500 mg/kg/day, corresponding to about 3

times the clinical exposure (based on AUC) at the maximum recommended clinical dose (MRCD).

Use in pregnancy - Category C

All anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and fetal loss. Bivalirudin had minimal effects on embryofetal development in rats and rabbits at SC doses up to 150 mg/kg/day (similar to the clinical exposure based on AUC at the MRCD). In rats, increased numbers of resorptions, decreased litter size, decreased fetal body weight, increased cervical rib and incomplete sternal ossification were observed at 500 mg/kg/day, a maternotoxic dose corresponding to about 3 times the clinical exposure based on AUC at the MRCD.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in lactation

SC administration of up to 150 mg/kg/day bivalirudin to lactating rats had no effects on pup development.

It is not known whether Angiomax[®] is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when Angiomax[®] is administered to a breastfeeding woman.

Use in children

The safety and effectiveness of Angiomax[®] in children have not been established.

Use in elderly patients

The relationship between age and bivalirudin pharmacodynamics has not been addressed directly, but in patients with normal renal function no differences in pharmacodynamics between patients above and below 65 years have been identified.

Since many elderly patients may have reduced renal function the anticoagulant status in elderly patients should be monitored and an Angiomax[®] dose adjustment should be considered based on the calculated GFR.

$$\text{GFR (mL/sec)} = \frac{(140 - \text{age (yrs)}) \times \text{weight (kg)}}{48,869 \times [\text{serum creatinine}] \text{ (mmol/L)}}$$

This value is to be adjusted for females by multiplying by 0.85.

Immunogenicity/Hypersensitivity

Allergic type hypersensitivity reactions were reported uncommonly 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 in post-marketing experience (see **ADVERSE EFFECTS**).

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.

Interactions with other drugs

Heparin

Patients can be started on Angiomax[®] 30 minutes after discontinuation of unfractionated heparin or 8 hours after discontinuation of low molecular weight heparin.

Other anticoagulants

Large scale studies support the concomitant use of bivalirudin with other anticoagulants commonly used during PCI (eg: acetylsalicylic acid (aspirin), ticlopidine, clopidogrel, abciximab, eptifibatide or tirofiban).

However, the combined use of anticoagulant drugs may increase the risk of bleeding. In any case, when bivalirudin is combined with a platelet inhibitor or an anticoagulant drug, clinical and biological parameters of haemostasis should be regularly monitored.

No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets. Ninety-six IV medications including those commonly administered to patients with coronary artery disease undergoing PCI were tested for Y-site physical compatibility with Angiomax[®].

It is known that the following drugs should **not** be administered in the same IV line with Angiomax[®]: *alteplase, amiodarone HCl, amphotericin B, chlorpromazine HCl, diazepam, prochlorperazine edisylate, reteplase, streptokinase and vancomycin HCl*. Use in the same IV line resulted in haze formation, microparticulate formation, or gross precipitation.

The chemical stability of bivalirudin or the additives in any admixtures has not been determined.

The following test drugs however are physically compatible with Angiomax[®]: *abciximab, dexamethasone sodium phosphate, digoxin, , dobutamine HCl (up to 4 mg/mL), dopamine HCl, adrenaline HCl, eptifibatide, esmolol, frusemide, heparin sodium, hydrocortisone sodium succinate, lignocaine HCl, pethidine HCl, methylprednisolone sodium succinate, midazolam HCl, morphine sulphate, , potassium chloride, sodium bicarbonate, tirofiban HCl, and verapamil HCl*.

Dobutamine, haloperidol lactate and promethazine HCl have been observed to have dose concentration incompatibilities with Angiomax[®] (Table 5).

Table 5. Drugs with dose concentration incompatibilities with Angiomax[®]

Drugs with dose concentration incompatibilities	Concentration at which compatibility has been demonstrated
Dobutamine	4 mg/mL
Haloperidol lactate	0.2 mg/mL
Lorazepam	0.5 mg/mL
Promethazine HCl	2 mg/mL

All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed in preparations of the parenteral drug products, these products should not be used with Angiomax[®].

Effects on the ability to drive and use machines

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

ADVERSE EFFECTS

Acute Coronary Syndrome (ACS) (the ACUITY trial)

The following adverse reaction data are based on a clinical study of bivalirudin in 13,819 patients with ACS; 4612 were randomised to bivalirudin alone, 4604 were randomised to bivalirudin plus GP IIb/IIIa inhibitor and 4603 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 drug reaction. Adverse events occurring in at least 1% of study patients in either the heparin or bivalirudin groups are listed by system organ class in Table 6.

Platelets, bleeding and clotting

In ACUITY, bleeding data were collected separately from adverse events. Major bleeding was measured by the ACUITY and TIMI major bleeding scales as defined in the footnotes to Table 7. 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 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 (see Table 7). Similar reductions in bleeding were observed in patients who were switched to bivalirudin from heparin-based therapies (N = 2078).

Table 6: ACUITY trial; adverse drug events occurring in at least 1% of study population administered heparin plus GP IIb/IIIa inhibitor or bivalirudin (either alone or plus GP IIb/IIIa inhibitor) – safety population

System organ class	Heparin ^a + Planned GP IIb/IIIa (N = 4696) (%)	Bivalirudin (N = 9028) (%)
Nervous system disorders		
Headache	3.0	3.1
Cardiac disorders		
Atrial fibrillation	1.1	1.0
Vascular disorders		
Minor bleeding	21.6	17.3
Major bleeding	5.7	4.2
Hypotension	1.7	1.6
Gastrointestinal disorders		
Nausea	2.1	2.4
Vomiting	1.0	1.0
Musculoskeletal and connective tissue disorders		
Back pain	2.9	2.8
Chest pain	3.7	3.4
General disorders and administration site conditions		
Pyrexia	1.1	1.1

Key: a: unfractionated heparin or enoxaparin

Adverse drug events occurring in less than 1% of the ACUITY study population administered heparin plus GP IIb/IIIa inhibitor, bivalirudin plus GP IIb/IIIa inhibitor, or bivalirudin alone include bradycardia, haemorrhage, vascular pseudoaneurysm, rash, urticaria, and injection site reactions.

Table 7: ACUITY trial; 30-day non-CABG bleeding endpoints for the ITT population.

	Arm A Heparin ^a + Planned GP IIb/IIIa (N = 4603) (%)	Arm B Bivalirudin + Planned GP IIb/IIIa (N = 4604) (%)	Arm C Bivalirudin (N = 4612) (%)	Arm C vs Arm A P-values
ACUITY major bleeding ^b	5.7	5.3	3.0	<0.0001
TIMI major bleeding ^c	1.9	1.7	0.9	0.0001
ACUITY minor bleeding	21.6	21.7	12.8	<0.0001
TIMI minor bleeding	6.4	6.1	3.7	<0.0001

Key: a: unfractionated heparin or enoxaparin

b: ACUITY major bleeding defined as any one of the following: intracranial, retroperitoneal, intraocular, access site haemorrhage requiring radiological or surgical intervention, ≥5cm diameter haematoma at puncture site, reduction in haemoglobin concentration of ≥4g/dL without an overt source of bleeding, reduction in haemoglobin concentration of ≥3g/dL with an overt source of bleeding, re-operation for bleeding, use of any blood product transfusion.

c: TIMI major bleeding defined as intracranial bleeding or a decrease in haemoglobin concentration ≥5g/dL

Major bleeding occurred most frequently at the sheath puncture site (see Table 8). Other less frequently observed bleeding sites with greater than 0.1% (uncommon) bleeding included “other” puncture site, retroperitoneal, gastrointestinal, ear, nose or throat.

Table 8: ACUITY trial; 30-day CABG and non-CABG bleeding site frequency data for the ITT population.

Bleeding site	Arm A Heparin ^a + Planned GP IIb/IIIa (N = 4603) (%)	Arm B Bivalirudin + Planned GP IIb/IIIa (N = 4604) (%)	Arm C Bivalirudin (N = 4612) (%)	Arm C vs Arm A P-values
Puncture site haematoma < 5 cm	7.5	7.4	4.5	<0.0001
Oozing blood at puncture site	8.5	7.7	3.8	<0.0001
Ecchymosis	5.8	6.0	3.7	<0.0001
Epistaxis	1.4	1.9	0.7	0.0012
Puncture site haematoma > 5 cm	2.2	2.2	0.7	<0.0001
Gingival Bleeding	0.6	1.5	0.3	0.1204
Genitourinary	0.9	1.1	0.3	0.0013
Gastrointestinal	0.9	0.7	0.5	0.0119
Sheath puncture site	0.5	0.7	0.4	0.2136
Retroperitoneal	0.5	0.6	0.2	0.0022
Hemoptysis	0.3	0.5	0.1	0.0046
Melena	0.4	0.3	0.3	0.2201
Ear, Nose or Throat	0.1	0.2	0.1	0.9975
Cardio/pulmonary	0.1	0.1	<0.1	0.1563
Intracranial	0.1	<0.1	<0.1	0.7034
Other	5.4	4.4	3.5	<0.0001

Key: a: unfractionated heparin or enoxaparin

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.

Percutaneous Coronary Intervention (PCI) (the REPLACE-2 trial)

The following adverse reaction data is based on a clinical study of bivalirudin in 6000 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 drug reaction. Adverse events occurring in at least 1% of the study population in either the heparin or bivalirudin groups are listed by system organ class in Table 9.

Table 9: REPLACE-2 trial; adverse drug reaction data events occurring in at least 1% of the study population administered heparin plus GP IIb/IIIa inhibitor or bivalirudin plus provisional GP IIb/IIIa inhibitor – safety population

System organ class	Heparin + Planned GP IIb/IIIa (N = 2987) (%)	Bivalirudin + Provisional GP IIb/IIIa (N = 2914) (%)
Blood and the lymphatic system disorders		
Thrombocytopenia	1.1	0.3
Nervous system disorders		
Headache	2.8	2.6
Insomnia	1.5	1.4
Cardiac disorders		
Ventricular tachycardia	0.9	1.0
Angina pectoris	5.2	5.3
Bradycardia	1.2	1.2
Hypertension	1.0	1.2
Hypotension	4.0	3.1
Vascular disorders		
Minor bleeding	25.8	13.6
Major bleeding	4.0	2.3
Gastrointestinal disorders		
Nausea	3.2	3.0
Musculoskeletal and connective tissue disorders		
Back pain	8.8	9.2
General disorders and administration site conditions		
Injection site pain	2.7	2.7
Chest pain	2.3	2.3
Abdominal pain	0.8	1.0
Pyrexia	0.5	1.0
Pain	2.4	3.4

Adverse drug events occurring in less than 1% of the REPLACE-2 study population administered heparin plus GP IIb/IIIa inhibitor or bivalirudin plus provisional GP IIb/IIIa inhibitor include anaemia, allergic reaction, thrombosis, haemorrhage, vascular disorder, vascular anomaly, dyspnoea, rash, and injection site haemorrhage.

Platelets, bleeding and clotting

In REPLACE-2, bleeding data were collected separately from adverse events.

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 (see Table 10). Other less frequently observed bleeding sites with greater than 0.1% (uncommon) bleeding included “other” puncture site, retroperitoneal, gastrointestinal, ear, nose or throat.

Table 10: REPLACE-2; bleeding site frequency data (bivalirudin versus heparin + GP IIb/IIIa inhibitor).

Bleeding site	Heparin +GP IIb/IIIa inhibitor (N=3008) (%)	Bivalirudin (N=2994) (%)	p-value
Sheath puncture site	2.5	0.8	0.001
Other puncture site	0.2	0.2	1.000
Retroperitoneal	0.5	0.2	0.062
Gastrointestinal	0.6	0.1	0.003
Ear, Nose or Throat	0.3	0.1	0.085
Genitourinary	0.2	<0.1	0.125
Intracranial	0.1	<0.1	1.000
Cardio/pulmonary	0.3	0.1	0.035
Other	0.5	0.4	0.556

Post-marketing experience

Adverse reactions that have been reported from post-marketing experience (more than 2,800,000 patients exposed) are summarised by system organ class in Table 11.

Table 10: Post-marketing adverse reactions reported for bivalirudin

System organ class	Frequency not known
Immune system disorders	Anaphylactic reaction, anaphylactic shock including fatal shock, hypersensitivity, urticaria
Vascular disorders	Thrombus including fatal thrombus. Serious bleeding, including haematoma and bleeding with a fatal outcome
Nervous system disorders	Intracranial haemorrhage

Heparin-Induced Thrombocytopenia/Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HIT/HITTS)

A clinical study evaluating the safety of bivalirudin in 52 patients with a prior diagnosis of HIT/HITTS, indicates 31% of the patients experienced an adverse event, and 6% a serious adverse event. The range and frequency of adverse events in HIT/HITTS patients is consistent with the PCI population, with no evidence of thrombosis syndromes or induction of thrombocytopenia.

DOSAGE AND ADMINISTRATION

Angiomax[®] is intended for use with aspirin (300-325 mg daily).

A P2Y₁₂ antagonist (eg clopidogrel or ticlopidine) may be used in addition to aspirin.

ACS

The recommended starting dose for patients with ACS is an IV bolus of 0.1 mg/kg followed by an infusion of 0.25 mg/kg/hour. Patients who are to be medically managed may continue the infusion of 0.25 mg/kg/hour for up to 72 hours.

If the patient proceeds to PCI, an additional bolus of 0.5 mg/kg should be administered at initiation of the PCI and the infusion increased to 1.75 mg/kg/hour for the duration of the procedure. Following the PCI, the reduced infusion dose of 0.25 mg/kg/hour may be resumed for 4 to 12 hours as clinically necessary.

PCI

The recommended dosage of Angiomax[®] for patients undergoing PCI is an IV bolus dose of 0.75 mg/kg followed by an IV infusion at a rate of 1.75 mg/kg/hour for the duration of the procedure, or for up to 4 hours post-PCI, as clinically indicated.

Treatment with Angiomax[®] should be initiated just prior to PCI.

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

Instructions for Administration

Angiomax[®] is intended for use as an IV bolus followed by an infusion (see **DOSAGE AND ADMINISTRATION**). The safety and efficacy of a bolus only dose of Angiomax[®] has not been evaluated and is not recommended even if a short PCI procedure is planned.

Angiomax[®] should be administered via an IV line. As with other parenteral anticoagulants, Angiomax[®] is not intended for intramuscular administration.

Angiomax[®] must be reconstituted and then diluted prior to administration of the IV bolus and the IV infusion. To reconstitute each 250 mg vial, add 5 mL of Water for Injections (WFI). Gently swirl contents in vial until all material is dissolved. Before administration, the contents of each reconstituted 250 mg vial should be diluted in 5% Glucose in Water or 0.9% Sodium Chloride for Injection up to a total volume of 50 mL (final bivalirudin concentration 5 mg/mL). To reconstitute each 100 mg vial, add 2 mL of Water for Injections (WFI). Gently swirl contents in vial until all material is dissolved. Before administration, the contents of each reconstituted 100 mg vial should be diluted in 5% Glucose in Water or 0.9% Sodium Chloride for Injection up to a total volume of 20 mL (final bivalirudin concentration 5 mg/mL).

Diluted Angiomax[®] at a concentration of 5 mg/mL is stable at room temperature for up to 24 hours.

The dose to be administered is adjusted according to the patient's weight.

The product should be administered within 24 hours of reconstitution and dilution to reduce microbiological hazard. If required it may be held at 2° to 8°C for up to 24 hours after reconstitution and dilution. Product is for one dose in one patient only. Any remaining contents should be discarded.

Reconstituted Angiomax[®] should be a clear to slightly opalescent, colourless to slightly yellow solution.

Renal Impairment

As Angiomax[®] is excreted by the kidneys, each individual's renal function should be considered prior to administration.

There is no clinical trial evidence regarding the safety and efficacy of Angiomax[®] in patients with creatinine clearance < 30 mL/min. The use of Angiomax[®] in these patients should occur only after careful consideration of the risks vs benefits (see **PRECAUTIONS**).

For patients with renal insufficiency not undergoing PCI, the ACS dose (0.1 mg/kg bolus and 0.25 mg/kg/hour infusion) should not be adjusted.

Dialysis-dependent patients and those with severe renal impairment (GFR<30 mL/min) proceeding to or undergoing PCI may need reduction of the infusion dose of Angiomax[®] as described in Table 1 (see **Pharmacokinetics**). No adjustment to the bolus dose is required. The anticoagulation status (ACT levels) may also need to be monitored in patients with renal impairment. Close, active clinical monitoring of the patient should also be considered.

Anticoagulants eliminated via renal mechanisms should be prescribed with caution for patients with moderate renal impairment (GFR 30-59 mL/min) as there is a higher risk of bleeding events.

Hepatic Impairment

Pharmacokinetic studies indicate that hepatic metabolism of bivalirudin is limited. Dose adjustment is not required.

Children

The safety and effectiveness of Angiomax[®] have not been studied in children.

OVERDOSAGE

Single bolus doses of Angiomax[®] up to 7.5 mg/kg have been reported. Bleeding has been observed in some reports of overdose.

In case of overdosage, Angiomax[®] should be discontinued and the patient should be closely monitored for signs of bleeding.

Discontinuation of Angiomax[®] leads to a gradual reduction in anticoagulant effects due to metabolism of the drug.

There is no known antidote to Angiomax[®].

Angiomax[®] is haemodialysable.

Approximately 25% bivalirudin is cleared by haemodialysis.

PHARMACEUTICAL PRECAUTIONS

Presentation

Angiomax[®] (bivalirudin) is available as a sterile, lyophilised product in single-use, glass vials.

100 mg Angiomax[®] Powder for Injection when reconstituted with 2 mL WFI yields a 50 mg/mL solution.

250 mg Angiomax[®] Powder for Injection when reconstituted with 5 mL WFI yields a 50 mg/mL solution.

Storage Conditions

Store below 25°C. Do not freeze.

Storage after Reconstitution

Do not freeze reconstituted or diluted Angiomax[®].

Reconstituted and diluted material may be stored at 2° to 8°C for up to 24 hours. Discard any unused portion of reconstituted solution remaining in the vial.

MEDICINE CLASSIFICATION

Prescription Only Medicine

PACAKGE QUANTITIES

Angiomax[®] is supplied in single-use vials as a white lyophilised cake, which is sterile. Each vial contains either: 250 mg bivalirudin present as bivalirudin trifluoroacetate (salt) hydrate and 125 mg mannitol; or 100 mg bivalirudin present as bivalirudin trifluoroacetate (salt) hydrate and 50 mg mannitol. Both presentations also contain sodium hydroxide.

FURTHER INFORMATION

Nil

NAME AND ADDRESS

Sponsor

CSL (New Zealand) Limited
666 Great South Road
Penrose, Auckland 6, NEW ZEALAND
Telephone: 09 579 8105

Manufactured by

Ben Venue Laboratories
Bedford, Ohio
United States of America

Supplier

The Medicines Company
Parsippany, NJ 07054
United States of America

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