CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-873

APPROVED LABELING

ANGIOMAX™ (bivalirudin) Injection

DESCRIPTION

Angiomax™ (bivalirudin) is a specific and reversible direct thrombin inhibitor. The active substance is a synthetic, 20 amino acid peptide. The 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 trifluoroacetate (salt) hydrate (Figure 1). The molecular weight of Angiomax ™ is 2180 daltons (anhydrous free base peptide). Angiomax ™ is supplied in single-use vials as a white lyophilized cake, which is sterile. Each vial contains 250 mg bivalirudin, 125 mg mannitol, and sodium hydroxide to adjust the pH to 5 to 6 (equivalent of approximately 12.5 mg sodium). When reconstituted with Sterile Water for Injection the product yields a clear to opalescent, colorless to slightly yellow solution, pH 5-6.

Figure 1. Structural Formula for Bivalirudin
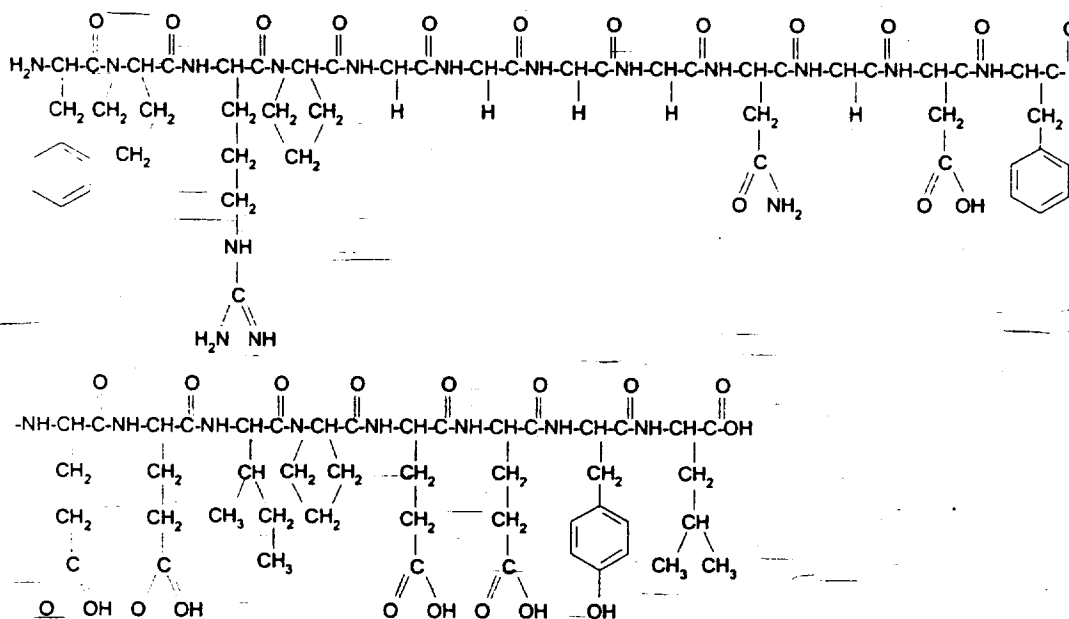
CLINICAL PHARMACOLOGY

General:
Angiomax™ directly inhibits thrombin by specifically 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, acting to cleave fibrinogen into fibrin monomers and to activate Factor XIII to Factor XIIIa, allowing fibrin to develop a covalently cross-linked framework which stabilizes 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 as thrombin slowly cleaves the Angiomax-Arg_3-Pro_4 bond, resulting in recovery of thrombin active site functions.

In in vitro studies, bivalirudin inhibited both soluble (free) and clot-bound thrombin, was not neutralized by products of the platelet release reaction, and prolonged the activated partial thromboplastin time (aPTT), thrombin time (TT),

and prothrombin time (PT) of normal human plasma in a concentration-dependent manner. The clinical relevance of these findings is unknown.

Pharmacokinetics:

Bivalirudin exhibits linear pharmacokinetics following intravenous (IV) administration to patients undergoing percutaneous transluminal coronary angioplasty (PTCA). In these patients, a mean steady state bivalirudin concentration of 12.3 ± 1.7 mcg/mL is achieved following an IV bolus of 1 mg/kg and a 4-hour 2.5 mg/kg/h IV infusion. Bivalirudin is cleared from plasma by a combination of renal mechanisms and proteolytic cleavage, with a half-life in patients with normal renal function of 25 minutes. The disposition of bivalirudin was studied in PTCA patients with mild and moderate renal function and in patients with severe renal function. Drug elimination was related to glomerular filtration rate (GFR). Total body clearance was similar for patients with normal renal function and with mild renal impairment (60-89mL/min). Clearance was reduced approximately 20% in patients with moderate and severe renal impairment and was reduced approximately 80% in dialysis-dependent patients. See Table 1 for pharmacokinetic parameters and dose reduction recommendations. For patients with renal impairment the activated clotting time (ACT) should be monitored. Bivalirudin is hemodialyzable. Approximately 25% is cleared by hemodialysis.

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

Table 1. PK parameters and dose adjustments in renal impairment			
Renal Function (GFR, ml/min)	Clearance (mL/min/kg)	Half-life (minutes)	% reduction in infusion dose
Normal renal function (≥90 ml/min)	3.4	25	0
Mild renal impairment (60-90 ml/min)	3.4	22	0
Moderate renal impairment (30-59 ml/min)	2.7	34	20
Severe renal impairment (10-29 ml/min)	2.8	57	60
Dialysis-dependent patients (off dialysis)	1.0	3.5 hours	90
* The ACT should be monitored in renally-impaired patients			

Pharmacodynamics:

In healthy volunteers and patients (with ≥ 70% vessel occlusion undergoing routine angioplasty), bivalirudin exhibits linear dose- and concentration-dependent anticoagulant activity as evidenced by prolongation of the ACT, aPTT, PT, and TT. Intravenous administration of Angiomax ™ produces an immediate anticoagulant effect. Coagulation times return to baseline approximately 1 hour following cessation of Angiomax ™ administration.

In 291 patients with ≥ 70% vessel occlusion undergoing routine angioplasty, a positive correlation was observed between the dose of Angiomax™ and the proportion of patients achieving ACT values of 300 sec or 350 sec. At an Angiomax™ dose of 1.0 mg/kg IV bolus plus 2.5 mg/kg/h IV infusion for 4 hours, followed by 0.2 mg/kg/h, all patients reached maximal ACT values > 300 sec.

Clinical Trials:

Angiomax™ was evaluated in patients with unstable angina undergoing PTCA in two randomized, double-blind,

multicenter studies with identical protocols. Patients must have had unstable angina defined as: (1) a new onset of severe or accelerated angina or rest pain within the month prior ɔ study entry or (2) angina or ischemic rest pain which developed between four hours and two weeks after an acute myocardial infarction (MI). Overall, 4312 patients with unstable angina, including 741 (17%) patients with post-MI angina, were treated in a 1:1 randomized fashion with Angiomax™ or heparin. Patients ranged in age from 29 –90 (median 63) years, their weight was a median of 80 kg (39-120kg), 68% were male, and 91% were Caucasian. Twenty-three percent of patients were treated with heparin within one hour prior to randomization. All patients were administered aspirin 300-325 mg prior to PTCA and daily thereafter. Patients randomized to Angiomax ™ were started on an intravenous infusion of Angiomax ™ (2.5 mg/kg/h). Within 5 minutes after starting the infusion, and prior to PTCA, a 1 mg/kg loading dose was administered as an intravenous bolus. The infusion was continued for 4 hours, then the infusion was changed under double-blinded conditions to Angiomax™ (0.2 mg/kg/h) for up to an additional 20 hours (patients received this infusion for an average of 14 hours). The ACT was checked at 5-minutes and at 45-minutes following commencement. If on either occasion the ACT was <350 seconds, an additional double-blinded bolus of placebo was administered. The Angiomax ™ dose was not titrated to ACT. Median ACT values were: ACT in seconds (5 th percentile-95th percentile): 345 sec (240 – 595 seconds) at 5 min and 346 sec (range 269– 583 sec) at 45 min after initiation of dosing. Patients randomized to heparin were given a loading dose (175 IU/kg) as an intravenous bolus 5-minutes before the planned procedure, with immediate commencement of an infusion of heparin (15 IU/kg/h). The infusion was continued for 4 hours. After 4-hours of infusion, the heparin infusion was changed under double-blinded conditions to heparin (15 IU/kg/hour) for up to 20 additional hours. The ACT was checked at 5-minutes and at 45 minutes following commencement. If on either occasion the ACT was <350 seconds, an additional double-blind bolus of heparin (60 IU/kg) was administered. Once the target ACT was achieved for heparin patients, no further ACT measurements were performed. All ACTs were determined with the Hemochron ® device. The protocol allowed use of open-label heparin at the discretion of the investigator after discontinuation of blinded study medication, whether or not an endpoint event (procedural failure) had occurred. The use of open-label heparin was similar between Angiomax™ and heparin treatment groups (about 20% in both groups).

The studies were designed to demonstrate the safety and efficacy of Angiomax ™ in patients undergoing PTCA as a treatment for unstable angina as compared with a control group of similar patients receiving heparin during and up to 24 hours after initiation of PTCA. The primary protocol endpoint was a composite endpoint called procedural failure, which included both clinical and angiographic elements measured during hospitalization. The clinical elements were: the occurrence of death, MI, or urgent revascularization, adjudicated under double-blind conditions. The angiographic elements were: impending or abrupt vessel closure. The protocol-specified safety endpoint was major hemorrhage.

The median duration of hospitalization was 4 days for both the Angiomax ™ treatment group and the heparin treatment group. The rates of procedural failure were similar in the Angiomax ™ and heparin treatment groups. Study outcomes are shown in Table 2.

Table 2. Incidences of In-hospital Clinical Endpoints In Randomized Clinical Trials Occurring Within 7 Days		
	ANGIOMAX™	HEPARIN
All Patients	n=2161	N=2151
Efficacy Endpoints:		
Procedural Failure[1]	7.9%	9.3%
Death, MI, Revascularization	6.2%	7.9%
Death	0.2%	0.2%
MI[2]	3.3%	4.2%
Revascularization[3]	4.2%	5.6%
Safety Endpoint:		
Major Hemorrhage[4]	3.5%	9.3%

[1] The protocol specified primary endpoint (a composite of death or MI or clinical deterioration of cardiac origin requiring revascularization or placement of an aortic balloon pump or angiographic evidence of abrupt vessel closure).
[2] Defined as: Q-wave MI; CK-MB elevation ≥ 2xULN, new ST- or T-wave abnormality, and chest pain ≥30 mins; OR new LBBB with chest pain ≥30 mins and/or elevated CK-MB enzymes; OR elevated CK-MB and new ST- or T-wave abnormality without chest pain; OR elevated CK-MB
[3] Defined as: any revascularization procedure, including angioplasty, CABG, stenting, or placement of an intra-aortic balloon pump.
[4] Defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, clinically overt bleeding with a decrease in hemoglobin ≥3 g/dL or leading to a transfusion of ≥2 units of blood.

INDICATIONS AND USAGE

Angiomax™ is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). Angiomax ™ is intended for use with aspirin and has been studied only in patients receiving concomitant aspirin (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

The safety and effectiveness of Angiomax™ have not been established when used in conjunction with platelet inhibitors other than aspirin, such as glycoprotein IIb/IIIa inhibitors. (See PRECAUTIONS, Drug Interactions).

The safety and effectiveness of Angiomax ™ have not been established in patients with unstable angina who are not undergoing PTCA or in patients with other acute coronary syndromes.

CONTRAINDICATIONS

Angiomax™ is contraindicated in patients with:
- active major bleeding;
- hypersensitivity to Angiomax™ or its components.

WARNINGS

Angiomax™ is not intended for intramuscular administration. Although most bleeding associated with the use of Angiomax™ in PTCA occurs at the site of arterial puncture, hemorrhage can occur at any site. An unexplained fall in blood pressure or hematocrit, or any unexplained symptom, should lead to serious consideration of a hemorrhagic event and cessation of Angiomax™ administration.

There is no known antidote to Angiomax™. Angiomax™ is hemodialyzable (See CLINICAL PHARMACOLOGY, Pharmacokinetics).

PRECAUTIONS

General:
Clinical trials have provided limited information for use of Angiomax™ in patients with heparin-induced thrombocytopenia/heparin-induced thrombocytopenia-thrombosis syndrome (HIT/HITTS) undergoing PTCA. The number of HIT/HITTS patients treated is inadequate to reliably assess efficacy and safety in these patients undergoing PTCA. Angiomax™ was administered to a small number of patients with a history of HIT/HITTS or active HIT/HITTS and undergoing PTCA in an uncontrolled, open-label study and in an emergency treatment program and appeared to provide adequate anticoagulation in these patients. In *in vitro* studies, bivalirudin exhibited no platelet aggregation response against sera from patients with a history of HIT/HITTS.

Drug Interactions:
Bivalirudin does not exhibit binding to plasma proteins (other than thrombin) or red blood cells.

Drug-drug interaction studies have been conducted with the adenosine diphosphate (ADP) antagonist, ticlopidine, and the glycoprotein IIb/IIIa inhibitor, abciximab, and with low molecular weight heparin. Although data are limited, precluding conclusions regarding efficacy and safety in combination with these agents, the results do not suggest pharmacodynamic interactions. In patients treated with low molecular weight heparin, low molecular weight heparin was discontinued at least 8 hours prior to the procedure and administration of Angiomax™.

The safety and effectiveness of Angiomax™ have not been established when used in conjunction with platelet inhibitors other than aspirin, such as glycoprotein IIb/IIIa inhibitors.

In clinical trials in patients undergoing PTCA, co-administration of Angiomax™ with heparin, warfarin or thrombolytics was associated with increased risks of major bleeding events compared to patients not receiving these concomitant medications. There is no experience with co-administration of Angiomax™ and plasma expanders such as dextran. Angiomax™ should be used with caution in patients with disease states associated with an increased risk of bleeding.

Pediatric Use:
The safety and effectiveness of Angiomax™ in pediatric patients have not been established.

Immunogenicity/Re-exposure:
Among 494 subjects who received Angiomax™ in clinical trials and were tested for antibodies, 2 subjects had treatment-emergent positive bivalirudin antibody tests. Neither subject demonstrated clinical evidence of allergic or anaphylactic reactions and repeat testing was not performed. Nine additional patients who had initial positive tests

were negative on repeat testing. —

Carcinogenesis, mutagenesis, and impairment of fertility:
No long-term studies in animals have been performed to evaluate the carcinogenic potential of Angiomax ™.
Bivalirudin displayed no genotoxic potential in the *in vitro* bacterial cell reverse mutation assay (Ames test), the *in vitro* Chinese hamster ovary cell forward gene mutation test (CHO/HGPRT), the *in vitro* human lymphocyte chromosomal aberration assay, the *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) assay, and 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, about 1.6 times the dose on a body surface area basis (mg/m ^{2}) of a 50 kg person given the maximum recommended dose of 15 mg/kg/day.

Pregnancy:
Angiomax™ is intended for use with aspirin (see INDICATIONS AND USAGE). Because of possible adverse effects on the neonate and the potential for increased maternal bleeding, particularly during the third trimester, Angiomax™ and aspirin should be used together during pregnancy only if clearly needed.

Pregnancy Category B:
Teratogenicity studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day, (1.6 times the maximum recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the maximum recommended human dose based on body surface area). These studies revealed no evidence of impaired fertility or harm to the fetus attributable to bivalirudin. There are, however, 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.

Nursing mothers:
It is not known whether bivalirudin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Angiomax™ is administered to a nursing woman. ⁻

Geriatric patients:
Of the total number of patients in clinical studies of Angiomax ™ undergoing PTCA, 41% were ≥65 years of age, while 11% were >75 years old. A difference of ≥5% between age groups was observed for heparin-treated but not Angiomax™-treated patients with regard to the percentage of patients with major bleeding events. There were no individual bleeding events which were observed with a difference of ≥5% between treatment groups, although puncture site hemorrhage and catheterization site hematoma were each observed in a higher percentage of patients ≥65 years age group than in patients < 65 years. This difference between age groups was more pronounced for heparin-treated than Angiomax™-treated patients.

ADVERSE REACTIONS

Bleeding:
In 4312 patients undergoing PTCA for treatment of unstable angina in 2 randomized, double-blind studies comparing Angiomax™ to heparin, Angiomax ™ patients exhibited lower rates of major bleeding and lower requirements for blood transfusions. The incidence of major bleeding is presented in Table 3. The incidence of major bleeding was lower in the Angiomax™ group than in the heparin group.

Table 3: Major bleeding and transfusions: All Patients [1]		
	ANGIOMAX™ N=2161	HEPARIN N=2151
No. (%) Patients with Major Hemorrhage[2]	79 (3.7)	199 (9.3)
- with ≥ 3g/dl fall in Hgb	41 (1.9)	124 (5.8)
- with ≥ 5g/dl fall in Hgb	14(<1%)	47(2.2)
- Retroperitoneal Bleeding	5 (<1%)	15 (<1%)
- Intracranial Bleeding	1(<1%)	2 (<1%)
- Required Transfusion	43 (2.0%)	123 (5.7%)

[1] No monitoring of ACT (or PTT) was done after a target ACT was achieved.
[2] major hemorrhage was defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, clinically overt bleeding with a decrease in hemoglobin ≥3 g/dl or leading to a transfusion of ≥2 units of blood. This table includes data from the entire hospitalization period.

Other adverse events:

In the 2 randomized double-blind clinical trials of Angiomax™ in patients undergoing PTCA, 81% of 2161 Angiomax™-treated patients and 83% of 2151 heparin-treated patients experienced at least one treatment-emergent adverse event. The most frequent treatment-emergent events were back pain (42%), pain (15%), nausea (15%), headache (12%), and hypotension (12%) in the Angiomax™-treated group. Treatment-emergent adverse events other than bleeding reported for ≥ 5% of patients in either treatment group are shown in Table 4.

Table 4. Adverse Events Other Than Bleeding Occurring In ≥ 5% Of Patients In Either Treatment Group In Randomized Clinical Trials.

EVENT	Treatment Group	
	ANGIOMAX™ (n=2161)	HEPARIN (n=2151)
	Number of Patients (%)	
Cardiovascular		
Hypotension	262 (12%)	371 (17%)
Hypertension	135 (6%)	115 (5%)
Bradycardia	118 (5%)	164 (8%)
Gastrointestinal		
Nausea	318 (15%)	347 (16%)
Vomiting	138 (6%)	169 (8%)
Dyspepsia	100 (5%)	111 (5%)
Genitourinary		
Urinary retention	89 (4%)	98 (5%)
Miscellaneous		
Back pain	916 (42%)	944 (44%)
Pain	330 (15%)	358 (17%)
Headache	264 (12%)	225 (10%)
Injection site pain	174 (8%)	274 (13%)
Insomnia	142 (7%)	139 (6%)
Pelvic pain	130 (6%)	169 (8%)
Anxiety	127 (6%)	140 (7%)
Abdominal pain	103 (5%)	104 (5%)
Fever	103 (5%)	108 (5%)
Nervousness	102 (5%)	87 (4%)

Serious, non-bleeding adverse events were experienced in 2% of 2161 Angiomax ™-treated patients and 2% of 2151 heparin-treated patients. The following individual serious non-bleeding adverse events were rare (>0.1% to <1%) and similar in incidence between Angiomax ™ and heparin-treated patients. These events are listed by body system: *Body as a Whole*: fever, infection, sepsis; *Cardiovascular*: hypotension, syncope, vascular anomaly, ventricular fibrillation; *Nervous*: cerebral ischemia, confusion, facial paralysis; *Respiratory*: lung edema; *Urogenital*: kidney failure, oliguria.

OVERDOSAGE

Discontinuation of Angiomax™ leads to a gradual reduction in anticoagulant effects due to metabolism of the drug. There has been no experience of overdosage in human clinical trials. In case of overdosage, Angiomax ™ should be discontinued and the patient should be closely monitored for signs of bleeding. There is no known antidote to Angiomax™. Angiomax™ is hemodialyzable. (See CLINICAL PHARMACOLOGY, Pharmacokinetics).

DOSAGE AND ADMINISTRATION

The recommended dosage of Angiomax ™ is an intravenous (IV) bolus dose of 1.0 mg/kg followed by a 4-hour IV infusion at a rate of 2.5 mg/kg/h. After completion of the initial 4-hour infusion, an additional IV infusion of Angiomax™ may be initiated at a rate of 0.2 mg/kg/h for up to 20 hours if needed. Angiomax ™ is intended for use with aspirin (300-325 mg daily) and has been studied only in patients receiving concomitant aspirin. Treatment with Angiomax™ should be initiated just prior to PTCA. The dose of Angiomax ™ may need to be reduced, and anticoagulation status monitored, in patients with renal impairment (See CLINICAL PHARMACOLOGY, Pharmacokinetics).

Instructions for Administration:
Angiomax™ is intended for intravenous injection and infusion. To each 250 mg vial add 5 ml of Sterile Water for Injection, USP. Gently swirl until all material is dissolved . Each reconstituted vial should be further diluted in 50 ml of 5% Dextrose in Water or 0.9% Sodium Chloride for Injection to yield a final concentration of 5 mg/mL (e.g., 1 vial in 50 mL; 2 vials in 100 mL; 5 vials in 250 mL.) The dose to be administered is adjusted according to the patient's weight, see table 5.

If the low-rate infusion is used after the initial infusion, a lower concentration bag should be prepared. In order to prepare this bag, reconstitute the 250 mg vial with 5 mL of Sterile Water for Injection, USP. Gently swirl until all material is dissolved. Each reconstituted vial should be further diluted in 500 mL of 5% Dextrose in Water or 0.9% Sodium Chloride for Injection to yield a final concentration of 0.5 mg/mL. The infusion rate to be administered should be selected from the right hand column in Table 5.

TABLE 5

DOSING TABLE

	Using 5 mg/ml concentration		Using 0.5 mg/ml concentration
Weight	Bolus (1 mg/kg)	Initial 4-hour Infusion (2.5mg/kg/hr)	Subsequent Low-rate Infusion (0.2mg/kg/hr)
(kg)	(ml)	(ml/hr)	(ml/hr)
43-47	9	22.5	18
48-52	10	25	20
53-57	11	27.5	22
58-62	12	30	24
63-67	13	32.5	26
68-72	14	35	28
73-77	15	37.5	30
78-82	16	40	32
83-87	17	42.5	34
88-92	18	45	36
93-97	19	47.5	38
98-102	20	50	40
103-107	21	52.5	42
108-112	22	55	44
113-117	23	57.5	46
118-122	24	60	48
123-127	25	62.5	50
128-132	26	65	52
133-137	27	67.5	54
138-142	28	70	56
143-147	29	72.5	58
148-152	30	75	60

Angiomax™ should be administered via an intravenous line. No other medications should be mixed with Angiomax™ before or during administration. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Preparations of Angiomax™ containing particulate matter should not be used.

Storage after Reconstitution:
Do not freeze reconstituted or diluted Angiomax ™. Reconstituted material may be stored at 2-8 °C for up to 24 hours. Diluted Angiomax ™ with a concentration of between 0.5 mg/mL and 5 mg/mL is stable at room temperature for up to 24 hours.

HOW SUPPLIED

Angiomax™ (bivalirudin) is supplied as a sterile, lyophilized product in single-use, glass vials. After reconstitution, each vial delivers 250mg of Angiomax™.

Reconstituted material will be a clear to slightly opalescent, colorless to slightly yellow solution.
Store Angiomax™ dosage units at 2-8°C.
Discard any unused portion of reconstituted solution remaining in the vial.

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TMC PN 1002, (insert date)

/s/

Victor Raczkowski
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