CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-873

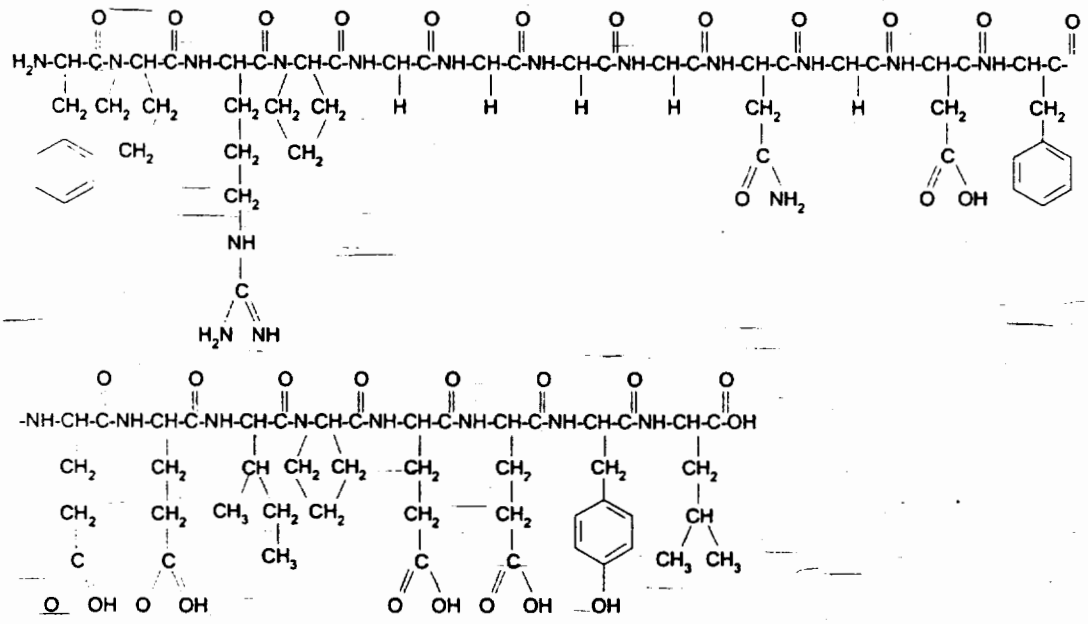
APPROVED LABELING

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 to 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

DOCKET ALARM

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