

## CLINICAL REVIEW

Application Type	NDA
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Priority or Standard	Standard
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Division / Office	DMIHP
Reviewer Name(s)	Saleh Ayache, MD
Review Completion Date	September 8, 2009
Established Name	Bivalirudin
(Proposed) Trade Name	Angiomax
Therapeutic Class	Anticoagulant
Applicant	The Medicines Company
Formulation(s)	250 mg single-use vial
Dosing Regimen	0.75 mg/kg IV bolus followed 1.75 mg/kg/h IV infusion for the duration of the procedure
Indication(s)	Anticoagulant used in patients receiving concomitant aspirin with 1) unstable angina undergoing PTCA or PCI and 2) with or at risk of HIT or HITTS, undergoing PCI.
Intended Population(s)	Pediatric (0-16 year)

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

(b) (4)



### 1.2 Risk Benefit Assessment

No deaths were reported during the course of this study. The procedure was successfully completed in (100%) of the patients.

Evaluation of bleeding events up to 30 days post-procedure showed that two patients (~1.9%) had a hematoma >2.5 cm that qualified as a major bleeding event and 12 patients (11%) had minor bleeding. Major bleeding incidence in the pediatric population (1.9%) was lower than in adults (2.2%). No correlation was demonstrated between the incidence of major and minor bleeding and the maximum ACT value (2 major and 5 minor bleeding events occurred in patients with ACT value < 350 seconds). However, additional exposure to the study drug with the administration of bivalirudin flush dose did not increase bleeding rates (4 minor and 1 major bleeding events occurred in patients who received Angiomax flush).


Thrombotic events up to 30 days post-procedure occurred in 8/106 (7.5%) patients in the per-protocol population (PP). Three events (all in infants) occurred during the procedure and five events occurred following discontinuation of study drug during the first follow-up period between 1.03 hours and 26.2 hours post procedure. There were no reports of thrombosis during the second follow-up period (48 h to 30 days). The thrombotic events occurred in arterial sheaths (n=3) and venous sheaths (n=4) in 7 patients, who had received saline flush all during (n=3) or immediately after (n=4) the bivalirudin infusion had been discontinued. The sheath thrombus in one patient who received a bivalirudin flush occurred during ASD closure in the Amplatzer® atrial septal occluder (ASO) femoral delivery sheath. Additionally, one thrombotic event occurred in the distal portion of the BT shunt post open heart surgery with heparin and was excluded from the thrombotic events. The results showed that using Angiomax flush (vs saline flush) has positive effects in preventing catheter thrombosis. However, there was no relationship between incidence of thrombosis and the maximum ACT value (4 thrombotic events occurred in patients with ACT value > 350 seconds).

The results also, revealed Angiomax effects on platelet counts in five patients who showed a decrease in platelet count from baseline to nadir of  $\geq 50\%$  ( $< 150,000/\mu\text{L}$ ) which occurred between Days 5 and 30.

There were 149 adverse events reported in 68 patients. However, twenty patients experienced adverse reactions deemed to be related to the drug; 14 with infusion site hemorrhage or hematoma, 3 with catheter sheath thrombosis, one with rash, and one with periorbital edema. One patient experienced vasospasm as a serious adverse reaction. The most frequently reported AEs were decreased pedal pulse, catheter site hemorrhage, abnormal pulse and nausea (8.2%, 7.3%, 6.4% and 5.5%, respectively).

In addition, there were six cases of adverse reactions reported as unrelated to the drug where we disagree with the causality assessment of the principal investigator (PI). Also, there were 14 additional cases of drug-related adverse events reported by the sponsor (11 cases of infusion site hemorrhage or hematoma, one case of catheter sheath thrombosis, one with rash, and one event of vasospasm).

The study demonstrated that Angiomax use as anticoagulant in pediatric patients as a weight-based IV bolus dose of 0.75 mg/kg followed by an infusion dose of 1.75 mg/kg/h, provides a target ACT between 200 and 400, without a significant increase in risk of bleeding or other safety concerns. (b) (4)



### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

(b) (4)

### **1.4 Recommendations for Postmarket Requirements and Commitments**

(b) (4)

## **2 Introduction and Regulatory Background**

Bivalirudin is a specific and reversible direct thrombin inhibitor. It is a synthetic 20 amino acid peptide. Bivalirudin indicated (initial approved December 15, 2000) for use as an anticoagulant: 1) in adult patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA), 2) with provisional use of glycoprotein IIb/IIIa inhibitors, is indicated for use in percutaneous coronary intervention (PCI), 3) for PCI in patients with heparin induced thrombocytopenia (HIT/HITTS). It has been studied only in patients concomitantly receiving aspirin.

The sponsor first submitted a Proposed Pediatric Study Request (PPSR) on March 3, 2006 to the Agency to perform a pediatric study to generate data in pediatric patients that would lead to dosing recommendations in children and to pediatric exclusivity for the sponsor. After a series of back and-forth negotiations, the Office of Oncology Drug Products issued a written request (WR) on May 7, 2007. The WR stated the type of study to be performed, the indications to be studied, the age distribution of the patients to be studied, the study evaluations and endpoints, the dosing regimen of the drug, safety evaluations to be assessed, the statistical analysis plan for the study, additional information to be provided, label changes to be considered, format of reports to be submitted, and the timeframe for submitting reports of the study.

The current submission contains the sponsor's response to the WR. The submission was reviewed for acceptability as having met the WR. (Pediatric exclusivity was granted on June 17, 2009).

The sponsor also proposes the following changes to the product labeling:

(b) (4)

(b) (4)



## 2.1 Review of the Submission

The submission consists of the following portions:

- A cover letter from the sponsor dated April 3, 2009 indicating the contents of the submission and a side-by side comparison of the requirements of the WR and the data generated by the study performed.
- Forms 356h, 3397, and 3674, 3542a
- A statement of claimed pediatric exclusivity
- A letter of authorization and cross reference to other NDA 20,873, IND 35,756, and IND (b) (4).
- A Request for Pediatric Exclusivity Determination.
- Written Agreement, and Other Correspondence Regarding Pediatric Exclusivity or Study Plans
- Environmental Analysis
- Request for categorical exclusion
- Label information (history label, current and a new draft label)
- A clinical study report (TMC- BIV -07 -01) entitled "Bivalirudin (Angiomax) as a Procedural Anticoagulant in the Pediatric Population Undergoing Intravascular Procedures for Congenital Heart Disease".
- A clinical overview, a summary of clinical effect and a summary of clinical safety for the study
- Integrated summary of efficacy



- Integrated summary of safety
- Literature references

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

Other drug used for anticoagulation in pediatric patients undergoing cardiac procedures is: Heparin.

## **2.3 Availability of Proposed Active Ingredient in the United States**

Angiomax (bivalirudin) is the only approved drug product in the U.S. having bivalirudin as active ingredient.

## **2.4 Important Safety Issues With Consideration to Related Drugs**

The following are the important listed adverse reactions in the Angiomax approved label:

- 1- Bleeding.
- 2- Thrombocytopenia.
- 3- Cardiovascular including hypotension, hypertension and bradycardia.
- 4- Other including back pain, pain at the injection site, insomnia, pelvic pain, anxiety, abdominal pain, fever, nervousness and headache.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The sponsor first submitted a request to the Agency to perform a pediatric study to generate data in pediatric patients that would lead to dosing recommendations in children and to pediatric exclusivity for the sponsor. After a series of back and-forth negotiations, the Office of Oncology Drug Products (Dr. Karen Weiss) issued a Proposed Pediatric Study Request (PPSR) on May 7, 2007. The PPSR stated the type of study to be performed, the indications to be studied, the age distribution of the patients to be studied, the study evaluations and endpoints, the dosing regimen of the drug, safety evaluations to be assessed, the statistical analysis plan for the study, additional information to be provided, label changes to be considered, format of reports to be submitted, and the timeframe for submitting reports of the study

## **2.6 Other Relevant Background Information**

None

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

The submission was adequately organized and presented.

#### **3.2 Compliance with Good Clinical Practices**

Informed consent from parents/legal guardians was obtained.

#### **3.3 Financial Disclosures**

There were 13 investigators (11 centers) for the study. The sponsor provided a certificate statement (form FDA 3454) indicating compliance with 21 CFR 54.

### **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

#### **4.1 Chemistry Manufacturing and Controls**

None

#### **4.2 Clinical Microbiology**

None

#### **4.3 Preclinical Pharmacology/Toxicology**

No juvenile/neonatal animal studies were done of the drug.

#### **4.4 Clinical Pharmacology**

[See Clinical Pharmacology Review (N. Mehratra, 9/10/2009)]

##### **4.4.1 Mechanism of Action**

Angiomax is a specific and reversible direct thrombin inhibitor.

#### 4.4.2 Pharmacodynamics

In healthy volunteers and patients (with  $\geq 70\%$  vessel occlusion undergoing routine angioplasty), Angiomax 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  $\geq 70\%$  vessel occlusion undergoing routine PTCA, 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.

#### 4.4.3 Pharmacokinetics

Angiomax exhibits linear pharmacokinetics following intravenous (IV) administration to patients undergoing percutaneous transluminal coronary angioplasty (PTCA). In these patients, a mean steady state Angiomax concentration of  $12.3 \pm 1.7$  mcg/mL is achieved following an IV bolus of 1 mg/kg and a 4-hour 2.5 mg/kg/h IV infusion. Angiomax 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 min. The disposition of Angiomax was studied in PTCA patients with mild and moderate renal impairment and in patients with severe renal impairment. 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 (60-89 mL/min). Clearance was reduced approximately 20% in patients with moderate and severe renal impairment and was reduced approximately 80% in dialysis dependent patients. For patients with renal impairment the activated clotting time (ACT) should be monitored. For dosing instructions, refer to the DOSAGE AND ADMINISTRATION section. Angiomax is hemodialyzable. Approximately 25% is cleared by hemodialysis.

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

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Study ID						
Study name Study design Country (no. sites)	Study start /Last patient completion dates	Patient population Control type		Sex (M/F)		
Location of study report	Total enrollment/ Enrollment goal	Duration of follow-up	Study drug Dose, route and regimen	Median age, Range	Anticoagulant effect variables	Outcomes/ Conclusion
TMC-BIV-07-01	15 August 2007	Pediatric patients	Bivalirudin IV	Male: 50	Thrombotic events, ACT	Thrombosis: 8.2%
Bivalirudin as a procedural anticoagulant in the pediatric population undergoing intravascular procedures for congenital heart disease	31 July 2008 Enrolled:110 Goal: 75	with congenital heart disease undergoing percutaneous coronary intervention	0.75 mg/kg bolus followed by IV infusion of 1.75 mg/kg/h for duration of procedure	Female: 60 Median age 3.96 years Range: 2 days -16.98 years	Bivalirudin plasma levels	ACT was generally similar in each of the age groups There was a general correlation between ACT and bivalirudin
procedures for congenital heart disease Prospective, open-labeled, single-arm, multicenter trial		Control: none Follow-up: 30 days or until resolution of SAE whichever was longer				plasma concentrations Bivalirudin provided safe anticoagulation at the adult weight-based dose of a 0.75 mg/kg IV bolus followed by a 1.75
US (11 centers)						mg/kg/h IV infusion.
TMC-BIV-02-04 Pilot Dose Finding and Efficacy Study Of Angiomax® (Bivalirudin) as Primary Anticoagulation in Infants Under Six Months With Thrombosis.	23 August 2002 / 11 February 2005 Enrolled:16 Goal: 25	2 US centers Patients < 6 months old with venous or arterial thrombus Control: None AEs through 14 days or discharge whichever was first, SAEs up to 30 days.	Initial bolus dose: 0.125 mg/kg, 0.25mg/kg or 0.5 mg/kg Initial infusion doses: 0.125 mg/kg/h or 0.25 mg/kg/h titrated to aPTT 1.5 to 2.5 times baseline for up to 14 days or discharge whichever was first.	Male: 7 Female 9 Median age: 43 days Range: 12 days – 197 days	Thrombus regression Thrombin generation markers aPTT Bivalirudin plasma levels (limited)	37.5% (6 patients) complete or partial thrombus resolution Reduction in levels of TAT, F1.2 and ddimer 15 of 16 patients attained target aPTT levels.

Source: sponsor submission.

## 5.2 Review Strategy

The major study for this supplement was Study TMC-BIV-07-01, “Bivalirudin (Angiomax) as a Procedural Anticoagulant in the Pediatric Population Undergoing Intravascular Procedures for Congenital Heart Disease”. The protocol and results for this study are

reviewed under Review of Efficacy (6) and Review of Safety (7) below. One supporting study TMC-BIV-02-04 also was submitted and is discussed under 5.3 below.

### **5.3 Discussion of Individual Studies/Clinical Trials**

The study TMC-BIV-02-04 was a “Pilot Dose Finding and Efficacy Study of Angiomax® (bivalirudin) as Primary Anticoagulation in Infants Under Six Months with Thrombosis”. The objectives of this open label, single group, multicenter study were to assess the safety of bivalirudin in infant under 6 months of age with arterial or venous thrombosis, to determine the dose of bivalirudin required to achieve adequate anticoagulation as measured by the activated clotting time (ACT) or activated partial thromboplastin time (aPTT) in this patient population and to determine the outcome of patients on bivalirudin with respect to thrombus resolution and bleeding complications as compared to patients on unfractionated heparin (UH) or low molecular-weight heparin (LMWH) based on historical data. Sixteen (16) infant subjects enrolled in the study with age from gestational age >35 weeks to <6 months in three cohorts. All patients received an initial bivalirudin IV bolus followed by an infusion. The bolus was 0.25 mg/kg in the first cohort (4 subjects) and 0.5 mg/kg in the second cohort (4 subjects), followed by an initial infusion of 0.25 mg/kg/h in both cohorts. The third cohort (8 patients) received an initial bivalirudin IV bolus dose of 0.125 mg/kg followed by an initial infusion of 0.125 mg/kg/h. The target ACT was 180-220 second and the target aPTT was 1.5 to 2.5 times baseline. If the ACT or aPTT was not achieved the infusion rate was increased or decreased in increments of 0.125 mg/kg/h until the target value was achieved. Bivalirudin administration commenced at the time of enrollment and continued for up to 14 days or discharge, whichever occurred first. Total duration of dosing ranged from 40.5 h to 350.5 h.

After initiating treatment with bivalirudin, all 3 molecular markers (d-dimer, thrombin-antithrombin complex [TAT], and prothrombin fragment 1.2 [F1.2]) of thrombin generation showed a reduction in their levels. The 3 different bolus doses achieved the target aPTT, and both initial infusion doses resulted in therapeutic aPTT values. The sponsor reports that thrombus was mostly resolved or showed some improvement in 6 of 16 patients (37.5%) after treatment with bivalirudin within 72 h. Six patients had complete or much restoration or some blood flow restored and 2 patients had a decrease in the diameter of an extremity or head. There were no deaths during the course of the study; investigators reported 1 patient as experiencing an SAE. There were no reports of intracranial hemorrhage or retroperitoneal hemorrhage. Major and minor bleeding events were reported in 75% (12/16) of the patients: seven patients had hematuria (3 with gross and 4 with microscopic hematuria), and five patients had a drop in Hb of >3 g/dL (2 major bleeding, 2 minor bleeding and one with no bleeding events). Thirteen patients (81%) experienced 1 or more AEs. Adverse events were assessed as drug related in 6 patients (37.5%) including one SAE reported as gross hematuria.

## 6 Review of Efficacy

### **Efficacy Summary**

Study TMC-BIV-07-01

#### **6.1 Indication**

The study was not an efficacy study. Bivalirudin was studied in pediatric patients undergoing intravascular procedures for congenital heart disease.

##### **6.1.1 Methods**

The major clinical study (TMC-BIV-07-01) was a prospective, open-labeled, single-arm, multicenter trial to assess the pharmacokinetics/pharmacodynamics (PK/PD) and safety of bivalirudin as a procedural anticoagulant in the pediatric population undergoing intravascular procedures for congenital heart disease.

At least 75 patients ranging in age from birth up to 16 years were to be enrolled, and complete treatment and study evaluations. At least 10 neonates (Birth ≤30days), 20 infants/toddlers (31 days to <24 months), 20 young children (2 years to <6 years) and 10 older children (6 years to <16 years) were to be included.

At least 50% of the cases in the study were to involve implantation of a device, either for closure of cardiac defects (such as atrial septal defect), or endovascular stenting (such as stenting of pulmonary vessels). The remaining procedures were to be diagnostic catheterizations, or other interventions such as balloon dilation procedures for treatment of aortic coarctation or valve stenosis.

Inclusion criteria includes males and females with an age range of birth to 16 years of age who will undergo a PCI for the management of congenital heart disease with life expectancy of at least 15 days at study entry.

Exclusion criteria were to exclude patients with a history of intracerebral bleed, GI or GU bleeding within the previous 2 weeks, CVA accident within the previous 6 months or a neurological deficit from any previous CNS event, acquired or congenital bleeding disorder, undergoing dialysis, weight <2.5 kg, received warfarin with INR >1.5 immediately prior to the procedure, using unfractionated heparin less than 30 minutes or LMW heparin < 8 hours prior to study drug bolus.

All patients were to receive bivalirudin at a starting dose of 0.75 mg/kg IV bolus followed by an IV infusion of 1.75 mg/kg/h for the duration of the procedure. At the investigator's discretion, a lower maintenance dose could be continued for up to 72 hours. If the patient's calculated glomerular filtration rate (GFR) was less than 30 mL/min (calculated

by the Counahan-Barratt formula), the continuous infusion dose was to be lowered to 1.0 mg/kg/h. Flushing of vascular insertion sheaths to keep insertion sheaths clear of thrombus and allow devices to be inserted through the vessel should be done with either 0.9% saline or a 0.1 mg/mL bivalirudin flush solution. No heparin was to be given for any other purpose during the course of the intervention, and if heparin was used prior to the procedure, it would have been discontinued for at least 8 hours for LMWH and 30 minutes for unfractionated heparin. Administration of concomitant medications, such as anti-platelet drugs, was at the discretion of the investigator.

Blood samples for the pharmacokinetic measurement of bivalirudin plasma concentrations should be collected pre-bolus, within the first 5 minutes post-bolus, at 30 minute intervals during the procedure, just before discontinuation of the bivalirudin infusion, and at 10 and 30 minutes after cessation of the infusion.

Bivalirudin concentrations should be measured by a validated liquid chromatography/mass spectrometry method. The pharmacodynamic effect of bivalirudin (ACT) was to be measured using a Hemochron<sup>®</sup> Jr. Signature Plus device at the same time points.

Patients should be monitored following drug administration for at least 30 days either during hospitalization or by telephone contact. Particular attention should be paid to bleeding and thrombotic events and all adverse reactions were to be collected. If the patient suffered a serious adverse reaction, the patient must be followed to resolution of the event. Endpoints should be assessed at discharge and at 30 days following the procedure.

### 6.1.2 Demographics

There were 10 patients from neonate group, 33 infants, 32 young children and 31 older children in the study. Patients were generally well distributed between males (46.2%) and females (53.8%). Non-white patients comprised 25.7% of the population; 7.7% were Hispanic or Latino.

### 6.1.3 Subject Disposition

A total of 110 patients enrolled at 11 centers in US between August 15, 2007 and July 31, 2008. Of the 110 patients enrolled 109 completed the study and 106 were treated according to protocol. All patients received bivalirudin and were included in the safety analysis population.

#### 6.1.4 Analysis of Primary Endpoint(s)

The per-population (N=106) was used for this analysis. The PK/PD results from the non-compartmental analysis of this pediatric study demonstrated that:

- Exposure to Angiomax was lower in pediatrics compared to adults receiving the same dose per weight regimen.
- The mean steady state concentration for pediatrics was 38 - 62% lower than the adults after the same dosing regimen.
- The effect on the activated clotting time (ACT) was found to be concentration dependent. The concentration-ACT relationship was not similar between pediatrics and adults. However, all pediatrics patients had ACT values within the target ranges in spite of lower steady state ACT than those in adults.
- The mean half-life for bivalirudin ranged from 15 to 18 minutes across all age groups (compared to 25 minutes in adults).

The PK/PD results are being reviewed by FDA Clinical Pharmacology.

#### 6.1.5 Analysis of Secondary Endpoints(s)

Analysis of the secondary endpoints including the incidence of bleeding and/or thrombotic events up to 30 days post-procedure and the changes in platelets count from baseline to end of the study as compared to the adult's studies revealed the following:

- There were no deaths during the course of this study.
- Analysis of bleeding events up to 30 days post-procedure showed that two patients (1.9%) had a hematoma >2.5 cm that qualified as a major bleeding event and 12 patients (11%) had minor bleeding. The incidence of major bleeding in the pediatric population (1.9%) was lower than in adults (2.2%).
- The incidence of thrombotic events up to 30 days post-procedure was 7.5% (8/106) of patients in the per protocol (PP) population. The occurrence of thrombotic events among patients who received Angiomax flush 1/53 was significantly lower than among those patients 7/57 who received saline flush. The thrombotic events occurred in arterial sheaths (n=3) and venous sheaths (n=4) in 7 patients, who had received saline flush all during (n=3) or immediately after (n=4) the bivalirudin infusion had been discontinued. The sheath thrombus in one patient who received a bivalirudin flush occurred during ASD closure in the Amplatzer® atrial septal occluder (ASO) femoral delivery sheath. Additionally, one thrombotic event occurred in the distal portion of the BT shunt post open heart surgery with heparin and was excluded from the thrombotic events.
- Five patients (one neonate, three infants and one young child) had a decrease from baseline to nadir platelet count of  $\geq 50\%$  and a nadir platelet count of less than 150,000/ $\mu\text{L}$ . Additionally, two older children had platelet counts below 150,000/ $\mu\text{L}$  at baseline and three had nadir counts below 150,000/ $\mu\text{L}$  but not a 50% decrease from baseline.



#### 6.1.6 Other Endpoints

N/A

#### 6.1.7 Subpopulations

There was a trend of an increase in mean maximum plasma concentration ( $C_{max}$ ), mean area under the concentration time curve (AUC<sub>0-t</sub>) and mean steady-state plasma concentration ( $C_{avg}$ ) with increasing age from neonates to older children when bivalirudin was administered as a weight-based dose. (See Clinical Pharmacology Review)

The PD response showed that younger pediatric patients, especially less than 6 months old are more sensitive to bivalirudin in terms of ACT response. Also, the ACT takes longer time to return to baseline following discontinuation of infusion in less than 6 month pediatric patients than all other groups.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

(b) (4)



#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The ACT takes longer time (8-12 h) to return to baseline following discontinuation of infusion in less than 6 month pediatric patients than all other groups (6-8 h). (See *Clinical Pharmacology Review, 9/11/2009 by Nitin Mehrotra*).

#### 6.1.10 Additional Efficacy Issues/Analyses

None.

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

A total of 110 patients were enrolled in Study TMC-BIV-07-01 (of 139 screened, 29 did not provide written consent) at 11 centers in the United States between August 15, 2007 and July 31, 2008. All patients received bivalirudin. Bivalirudin administration was initiated at the start of the interventional procedure with a 0.75 mg/kg IV bolus followed by an IV infusion of 1.75 mg/kg/h for the duration of the procedure.

All subjects were evaluated for the incidence of bleeding including major and minor bleeding, the incidence of thrombosis, platelet count changes and the incidence of any adverse events occurring during the procedure through 30 after the procedure. All these safety parameters were collected through reviewed case report forms and clinical laboratory listing.

Detailed results of the safety parameters are described in section (6.1.5).

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study TMC-BIV-07-01 is a prospective, open-labeled, single-arm, multicenter trial to assess the pharmacokinetics/pharmacodynamics (PK/PD) and safety of bivalirudin as a procedural anticoagulant in the pediatric population undergoing intravascular procedures for congenital heart disease.

Study TMC-BIV-02-04 was not included in the safety evaluation since this study was conducted to evaluate, the safety of Angiomax in patients less than six months old with arterial and venous thrombosis and the efficacy of Angiomax in respect to thrombus resolution.

#### 7.1.2 Categorization of Adverse Events

- Incidence of thrombosis during the procedure through 30 days.
- Incidence of bleeding complications during the procedure through 30 days.
- Changes in platelet count occurring during the procedure through 30 days.
- Other adverse events occurring during the procedure through 30 days.

#### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

### 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Bivalirudin was administered as an IV bolus (110 patients) followed by an IV infusion (109 patients) for the duration of the interventional procedure in accordance with the clinical study protocol. The mean average weight-based bolus dose was  $0.75 \pm 0.014$  mg/kg. However, one patient received a second bolus due to a delay in the infusion reaching the patient.

The mean average drug infusion dose rate was  $1.738 \pm 0.108$  mg/kg/h. However, one patient's infusion dose was recorded as 0.75 mg/kg/h and one neonate patient received a bolus dose but mistakenly did not receive the intended infusion during the procedure due to pump malfunction. This patient subsequently received a low-dose post-procedural infusion of 0.24 mg/kg/h for 22.7 hours. The overall mean average drug exposure was  $58.524 \pm 66.475$  mg.

Access lines were flushed with a fixed 0.1 mg/mL bivalirudin solution in 53/110 (48.2%) of patients at a mean dose of  $12.189 \pm 10.722$  mg. Flush dose was calculated by the volume of flush solution used from the flush bag from the beginning to the end of procedure. The average mean total duration of exposure to infusion across all age groups was  $1.18 \pm 2.218$  hours. One patient (102006) received low dose study drug for 22.7 hours. The majority of patients (80/110) were exposed to study drug for  $\leq 1$  hour.

### 7.2.2 Explorations for Dose Response

Dose response was not studied.

### 7.2.3 Special Animal and/or In Vitro Testing

N/A

### 7.2.4 Routine Clinical Testing

Clinical laboratory testing for PK and ACT were done at pr-bolus, within the first 5 minutes post bolus, at 30 minutes interval during the procedure, just before discontinuation of Angiomax infusion, and at 10 and 30 minutes after cessation of the infusion. The clinical study assessments were performed as shown in Table 1.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A

### 7.3 Major Safety Results

#### 7.3.1 Deaths

There were no deaths reported in the study.

#### 7.3.2 Nonfatal Serious Adverse Events

The only serious adverse event reported as drug related was a case of vasospasm. No safety signals were detected in this pediatric population.

#### 7.3.3 Dropouts and/or Discontinuations

No patients discontinued or withdrew from treatment due to AEs.

#### 7.3.4 Significant Adverse Events

The AEs reported in this study were consistent with the disease state and treatment of these critically ill patients. Adverse events were reported in approximately 62% (68/110) of subjects in the study with a total of 149 adverse events. However, twenty patients (18%) experienced adverse reactions deemed to be related to the drug including: 14 with infusion site hemorrhage or hematoma, 3 with catheter sheath thrombosis, one with rash, and one with periorbital edema. One patient experienced vasospasm as a serious adverse reaction.

#### 7.3.5 Submission Specific Primary Safety Concerns

The primary safety concerns in this application are bleeding and thrombosis.

### 7.4 Supportive Safety Results

#### 7.4.1 Common Adverse Events

The most frequently reported AEs were decreased pedal pulse, catheter site hemorrhage, abnormal pulse and nausea (8.2%, 7.3%, 6.4% and 5.5%, respectively).

AEs occurred more frequently in neonates 10/11 (91%) and infants 20/33 (61%) than in older children 17/34 (50%). There were 149 reported AEs which occurred in 68 subjects; 20 were assessed as related to the drug. The AEs were assessed to be related to the drug are twenty patients experienced adverse reactions deemed to be: 14 with infusion site hemorrhage or hematoma, 3 with catheter sheath thrombosis, one with rash, one with vasospasm and one with periorbital edema. Most of these adverse events occurred either during or shortly post procedure.

The sponsor reported that 14/149 are related to the drug, however an additional 6 adverse events we think may possibly be related to study treatment are listed below:

#### Case # 1

A four-year-old female received bivalirudin during a procedure to close the atrial septal defect (ASD) with Amplatzer occluder. The procedure and the recovery were uneventful without bleeding noted. A right femoral sheath thrombosis was found in the catheter sheath when removed 30 minutes after the procedure. The PI determined the event was unrelated to study drug. I think there is a possibility that the adverse reaction is drug related and may have been due to inadequate or insufficient anticoagulant effect.

#### Case# 2

A six-year-old female received bivalirudin during a procedure to close an ASD with Amplatzer occluder. During the procedure the subject experienced an episode of supraventricular tachycardia which resolved within 21 minutes. A thrombus in the right femoral venous sheath was noted 10 minutes after the Angiomax was stopped. Also, a mild bleeding was noted at the location of the sheath in the recovery room. The PI determined that both events were unrelated to bivalirudin therapy. However, I think there is a possibility that the mild bleeding at the location of the sheath may have been due to the anticoagulant effect of the drug.

#### Case #3

A seventeen-day-old male neonate with a history of aortic valve stenosis was enrolled in bivalirudin pediatric study on 12NOV07. Aortic valvuloplasty was performed. The subject was stable during the procedure; however 30 minutes into the procedure the PI noted that the IV infusion of bivalirudin was not delivered due to mechanical failure of IV pump. No Angiomax rebolus was done since the PI considered the case finished at that time. Small pieces of thrombi were noted in the arterial sheath at sheath removal. The procedure was uneventful and no bleeding was noted.

The adverse event was reported by the PI as unrelated to the study drug. However, we disagree with that assessment and I think there is a possibility that the thrombosis event is related to inadequate anticoagulant effect of the drug. It is not clear exactly how much bivalirudin the subject actually received.

#### Case #4

A five-year-old female received Angiomax during a procedure of atrial septal defect closure with Amplatzer occluder. Post-procedure the subject experienced an episode of nausea and vomiting which resolved without incident. Additionally, the subject had a small amount of bleeding at the femoral sheath site, and two small hematomas were found at the sheath insertion site when the pressure dressing was removed. The day after the procedure the subject's temperature was elevated slightly but returned to normal without complication.

We disagree with the PI who reported that both the mild bleeding and the hematoma at the site of the sheath insertion were unrelated. The events may have been due to anticoagulant effect of the drug.

#### Case #5

A twenty-five-day-old female neonate received Angiomax during a pulmonary valvuloplasty procedure. The procedure was uneventful and no thrombus was noted. Post-procedure minor bruising was noted at the right groin access site.

We disagree with the PI who reported that the catheter site hematoma was unrelated. The event may have been due to anticoagulant effect of the drug.

#### Case #6

A three-month-old female received Angiomax during aortic valvuloplasty procedure. No bleeding or thrombus was noted during the procedure. Post-procedure, 3 hours and 13 minutes after study drug discontinuation, subject experienced a drop in hct resulting in a transfusion of 60 mL packed red blood cells (PRBCs). The attending MD noted that hematocrit drop was related to the fragile status of the subject and not related to a bleeding event. Also, the subject had episodes of periorbital edema and airway congestion both of which resolved the next day. Subject also was agitated the day after the procedure, which lasted one hour and 10 minutes. Subject recovered from all events without complication.

### 7.4.2 Laboratory Findings

Platelets counts: five patients (1 neonate, 3 infants and 1 young child) had nadir platelet counts that were below 150,000/ $\mu$ L and decreased by 50% from baseline with all occurred between Day 5 and 30. All these five patients had a normal baseline platelet counts.

Hemoglobin and Hematocrit: Hb and HCT were measured during the procedure, post procedure and in the follow up period. The mean average Hb changes from baseline to 48 hour post baseline showed a dropped of mean average of  $1.71 \pm 1.36$  g/dL, and  $1.42 \pm 1.03$  g/dL in the period from 48 hour post baseline to the final evaluation period.

### 7.4.3 Vital Signs

Vital signs represent a variety of baseline values consistent with the complex cardiology of these patients. Changes in blood pressure and heart rate from baseline to nadir values were unremarkable.

### 7.4.4 Electrocardiograms (ECGs)

No ECGs results were reported.

### 7.4.5 Special Safety Studies/Clinical Trials

N/A

### 7.4.6 Immunogenicity

N/A

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Only one dose regimen was tested in this study.

### 7.5.2 Time Dependency for Adverse Events

Two major bleeding events were hematoma > 2.5 cm. The first case of hematoma occurred at the venous sheath site 35 minutes post procedure in a patient who received a total dose of 40.77mg of bivalirudin during a procedure lasting 54 minutes. The second hematoma occurred 1 hour post procedure after removal of a Boomerang closure device at the arterial and venous sheath site in a patient who received a total dose of 238.78 mg of bivalirudin during a procedure lasting 2 hours.

Minor bleeding mostly occurred after the procedure and primarily in children between the ages of 2-6 years (10 of 12 events) and mainly occurred at the catheterization site.

Thrombotic events mainly occurred after the procedure completion in the catheter sheath.

AEs occurred more frequently in neonates 10/11 (91%) and infants 20/33 (61%) than in older children 17/34 (50%). There were 149 reported AEs which occurred in 68 subjects; 20 were assessed as related to the drug. Most of these adverse events occurred either during or shortly post procedure.

The PI assessment reported that the periorbital edema and the drop in hematocrit were unrelated and provides explanation to the reason for hemoglobin drop; however the PI did not provide explanation to the cause of periorbital edema.

### 7.5.3 Drug-Demographic Interactions

N/A

### 7.5.4 Drug-Disease Interactions

Procedures in all patients were completed as planned. Five (4.7%) patients had procedural complications unrelated to bleeding or thrombotic events.

### 7.5.5 Drug-Drug Interactions

N/A

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

N/A

### 7.6.2 Human Reproduction and Pregnancy Data

N/A

### 7.6.3 Pediatrics and Assessment of Effects on Growth

N/A

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

## 7.7 Additional Submissions / Safety Issues

The safety results from TMC-BIV-20-04 study showed that no deaths occurred among the 16 study subjects. However there was high incidence of bleeding 75% experienced at least 1 or more bleeding events (5 major bleeding, and 7 with minor bleeding). There were 38 adverse events reported in 13 patients (81%) and these mostly occurred during



the drug infusion (14 day). 12/38 (32%) of the adverse events were considered related to the drug with only one serious adverse reaction (gross hematuria).

## **8 Postmarket Experience**

The OSE examination of the AERS database for pediatric reports is pending.

## 9 Appendices

### 9.1 Literature Review/References

The literature review done by the sponsor (confirmed by my search in PubMed) found reports of the successful use of bivalirudin as an anticoagulant in a total of 69 pediatric patients. There were eight citations; five represented original clinical research/case reports and are presented in this report; two were review articles and one was an in vitro study; these are not included in this report. Bivalirudin was used in 33 pediatric patients undergoing interventional cardiac procedures to prevent thrombosis and as a treatment for thrombosis in 36 patients.

Demographics: Patients treated for thrombosis ranged in age from 0.03 month (<1 day) to 14 years; 19 males and 13 females. Patients weighed from 3 kg to 55 kg. Those patients requiring prevention of thrombosis during a wide range of cardiac procedures ranged in age from 5 days to 25 years.

Dosing: There is no consistent dosing regimen reported in the literature, either for the treatment or the prevention of thrombosis. For treatment of thrombosis, bolus doses were not administered in 7 patients, and ranged from 0.06 mg/kg to 0.5 mg/kg in the remaining patients. The average infusion doses ranged from 0.05 mg/kg/h to 0.31 mg/kg/h. These doses were titrated against a desired increase of the patients' activated partial thromboplastin time (aPTT), often for several days. For use as an anticoagulant in interventional cardiac procedures, bolus doses ranged from 0.15 mg/kg to 0.75 mg/kg and infusion doses ranged from 0.25 mg/kg/h to 1.75 mg/kg/h. These infusions were used during the procedure only. Bivalirudin doses for extracorporeal membranous oxygenation (ECMO) circuits ranged from 0.05 to 0.65 mg/kg/h.

Summary of Clinical Outcomes: In studies of thrombosis treatment, patients who received bivalirudin had clot regression in 10/10 patients who had follow-up imaging in one study <sup>(1)</sup> and in 6/16 <sup>(2)</sup> in another study. Hematuria was reported in three patients with indwelling catheters. No other treatment related adverse events were reported. For anticoagulation in interventional procedures, there were no reports of significant clot or thrombosis, catheter clot formation was observed in one patient; one episode of bleeding was reported following separation from cardiopulmonary bypass <sup>(3-6)</sup>. From these published reports in children, bivalirudin appears to act in a manner similar to that in adults when measured directly by imaging of clot regression and absence of thrombus and indirectly by prolongation of activated clotting time (ACT) or aPTT. Using these pharmacodynamic (PD) measures [ACT (when using higher doses), and aPTT (when using lower doses)] confirms that a patient is receiving anticoagulation but the PD parameters offered little guidance to reliably indicate an appropriate dose across the spectrum of ages and variety of indications.

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## 9.2 Labeling Recommendations

(b) (4)



Clinical Review  
{Saleh Ayache}  
{NDA 20873 Pediatric exclusivity}  
{Angiomax}

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(b) (4)



### **9.3 Advisory Committee Meeting**

N/A

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20873	SUPPL-19	THE MEDICINES CO	ANGIOMAX

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/s/

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SALEH AYACHE  
10/23/2009

KATHY M ROBIE SUH  
10/27/2009

OSE examination of AERS database is pending. Exact wording in labeling is being negotiated with the sponsor.