DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

NDA 20-873
IND 35,756

WRITTEN REQUEST

The Medicines Company
Attention: Gary Knappenberger
Sr. Director, Regulatory Affairs
8 Campus Drive
Parsippany, NJ 07054

Dear Mr. Knappenberger:

Reference is made to your February 5, 2007, revised Proposed Pediatric Study Request (PPSR) submitted to IND 35,756 for Angiomax (bivalirudin), in response to the December 15, 2006 information request letter issued by the FDA. Reference is also made to your PPSR submitted March 3, 2006, the dispute resolution meeting held September 27, 2006, and the revised PPSR submitted November 9, 2006.

To obtain needed pediatric information on Angiomax (bivalrudin), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following study:

- ***Type of study:***
  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.

- ***Indications to be studied:***
  Use of bivalirudin as an anticoagulant in pediatric patients during percutaneous intravascular procedures for the management of congenital heart disease. The study objectives are as follows:
  - To determine the plasma concentrations of bivalirudin following administration of doses described below in pediatric subjects;
  - To determine the PD (as measured by the activated clotting time [ACT]) of bivalirudin following administration of doses described below in pediatric patients;
  - To provide dosing guidelines for the use of bivalirudin as an anticoagulant during percutaneous intravascular procedures in pediatric patients;
  - To evaluate the safety of bivalirudin in pediatric patients by evaluating bleeding, thromboses and other serious adverse events.

At least 50% of the cases in the study will involve implantation of a device, either for the treatment of atrial septal defect or patent ductus arteriosus, or for stenting of pulmonary vessels. The remainder of the procedures will be diagnostic catheterization, or balloon angioplasty to treat lesions such as aortic coarctation or valve stenosis.

- ***Age groups and numbers of patients in which study will be performed:***
  - Neonates (birth to <1 month old)
  - Infants/toddlers (1 to <24 months)
  - Young children (2 to <6 years)
  - Older children (6 to <16 years)

At least 75 patients ranging in age from birth up to 16 years, and including at least 10 neonates, 20 infants/toddlers, 20 young children and 10 older children, will complete treatment and study evaluations.

- ***Study evaluations and endpoints:***

The study evaluations are as follows:

- The pharmacokinetics and pharmacodynamics of bivalirudin;
- The incidence of bleeding and/or thrombotic events up to 30 days post procedure (If a patient experiences a serious adverse event (SAE) he/she will be followed to resolution of the SAE);
- Changes in platelet count from baseline to end of study.

Pharmacokinetic assessments:
Plasma bivalirudin concentrations will be determined in pediatric patients using a validated method.

Pharmacodynamics:
ACT will be measured with a Hemochron® device using blood obtained at the same time and from the same source line that will be used for PK samples.

Bleeding events:
The major safety evaluation concerns bleeding. The occurrence of major and minor hemorrhage up to 30 days post procedure will be assessed (If a patient experiences a serious adverse event he/she will be followed to SAE resolution). In addition to any other criteria for defining "hemorrhage," the protocol will cite the following definitions:

The definition of "major hemorrhage" includes any one of the following events:

- Intracranial hemorrhage
- Intraocular hemorrhage
- Retroperitoneal hemorrhage

- Gross hematuria
- Drop in hemoglobin of >3 g/dL with overt blood loss
- Bleeding that necessitates a blood transfusion
- Hematoma (of a size or consequence as specified in the protocol)

Adverse events:
Serious adverse events and events of special interest (thrombosis in the canulated vessel(s) and at the cardiac/pericardiac site of manipulation/implantation) will be ascertained. The occurrence of such events up to 30 days post procedure will be assessed. All other adverse reactions occurring up to 30 days post procedure will also be assessed. If a patient experiences a serious adverse event (SAE) he/she will be followed to resolution of the SAE.

Timing of Assessment:
Patients will be monitored closely during the procedures and for the first 48 hours post procedure or until hospital discharge. Follow-up will continue for at least 30 days. If a patient experiences a serious adverse event (SAE) he/she will be followed to resolution of the SAE), whichever is longer.

Blood samples for measurement of bivalirudin plasma concentrations and ACT will be collected pre-bolus, immediately (or within the first 5 minutes) post-bolus, at approximately 30-minute intervals during the procedure, just before discontinuation of the bivalirudin infusion (when discontinuation is longer than approximately 10 minutes after the previous sample), and at approximately 10 and approximately 30 minutes after the last infusion. Blood draws should be done using the smallest amount of blood possible and in accordance with guidelines established by the IRB.

Each time the dose is changed, plasma samples for bivalirudin concentration and ACT will be collected at steady state or just before discontinuation of the bivalirudin infusion.

Inclusion Criteria:
Patients will be males and non-pregnant females with an age range of 0 up to 16 years of age who are expected to undergo an elective percutaneous intravascular procedure for the management of congenital heart disease. Written informed consent from a legal guardian/parent will be obtained.

Exclusion Criteria of particular importance are:
- Known history of intracerebral bleed;
- Known congenital or acquired bleeding or clotting disorder;
- Patients undergoing renal dialysis;
- Patients with a body weight less than 2.5 kg.

- ***Drug information***

  Dosage form:
  The dosage form and packaging will be identical to the product available for adult patients. Each vial contains 250 mg bivalirudin, 125 mg mannitol, and sodium hydroxide to adjust for pH.

  Route of administration: Intravenous

  Regimen:
  The dosing regimen will be:
  - Patients with glomerular filtration rates (GFR) $\geq$ 30 mL/min, will receive an IV bolus dose of 0.75 mg/kg immediately followed by an IV infusion of 1.75 mg/kg/h for the duration of the procedure;
  - Patients with GFR < 30 mL/min will receive an IV bolus of 0.75 mg/kg immediately followed by an IV infusion of 1.0 mg/kg/h for the duration of the procedure.

  In each pediatric age group, after the first 5 patients have been studied, the data must be evaluated for consideration of the need for adjustment of the dose of bivalirudin for that age group to achieve an appropriate target plasma concentration level.

  Investigators will have the option of providing a maintenance dose of 0.25 mg/kg/h for as long as necessary post-procedure for up to 72 hours. Bivalirudin will be started at the beginning of the interventional procedure with a bolus dose followed by infusion.

  The protocol will specify any plans for alteration of the dosages for each patient during the percutaneous procedure based upon ACT findings.

- ***Drug specific safety concerns:***
  Concerns relate predominantly to bleeding and possible prolonged bivalirudin effects in neonates because of immaturity of liver function; another consideration is the possible local irritant effects of the drug. Adverse events (including clinical outcomes of thrombosis and bleeding) as well as pertinent clinical laboratory studies (including platelet counts) will be collected and reported for all patients.

  There will be an independent Data Safety Monitoring Committee established to regularly examine the safety data during the conduct of the study. A charter will be developed to describe the composition of the Committee, the types of data to be presented to the Committee and the Committee responsibilities. The Charter will, in addition to any other items, specify that the Committee will be authorized to recommend modifications to the study protocol in order to optimize safety.

Renal function:
Immature renal function is commonly present in children younger than 1 year but a glomerular filtration rate (GFR) >30 mL/min is usually present by the end of the first month of life. Accordingly, the infusion dose may be reduced as appropriate in younger pediatric populations if so indicated as data is collected. Renal function will be assessed prior to the procedure and if the GFR <30 mL/min, the infusion will be reduced as described above. Patients dependent on renal dialysis will be excluded from the study.

- ***Statistical information:***
  Population Pharmacokinetic/Pharmacodynamic (PK/PD) analysis of bivalirudin concentration – ACT data will be conducted in pediatric patients and compared with that of adults.

  A descriptive analysis of outcomes will be compiled, particularly in regard to the success or failure of the performance of the procedure. Line listings of adverse events will be provided. Descriptive analyses of adverse events and other safety data will be compiled. In cases of bleeding events, change in hematocrit between baseline and the lowest value will be determined.

- ***Additional information needed:***
  The study report will include a thorough review of the medical literature and any other sources of information on the use of bivalirudin in pediatric patients and provide a critical analysis and summary, integrating these findings with the findings from this PK/PD, safety study.

- ***Labeling that may result from the study:***
  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- ***Format of reports to be submitted:***
  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All patients enrolled in the study will be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White. For ethnicity, one of the following designations will be used: Hispanic/Latino or Not Hispanic/Latino. Please submit the following to support the concentration-ACT relationship derived from population PK/PD analysis in adults and pediatric patients:

  - All datasets used for population PK/PD model development and validation will be submitted as a SAS transport files (*.xpt). A description of each data item will be provided in a Define.pdf file.

Any concentrations, ACT and/or patients that have been **excluded from the analysis** will be flagged and maintained in the datasets.

- Population PK/PD model codes or control streams and output listings will be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files will be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

- A population PK/PD model development decision tree and/or table which gives an overview of modeling steps.

For the analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of patients. Each individual plot must include observed concentrations/ACT, the individual predication line and the population prediction line. In the report, tables must include model parameter names and units. For example, clearance must be presented as CL (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

- ***Timeframe for submitting reports of the study:***
  Report of the above study must be submitted to the Agency on or before September 30, 2009. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

- ***Response to Written Request:***
  As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC**

STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Patricia Stewart, Regulatory Health Project Manager, at 301-796-1469.

Sincerely,

{See appended electronic signature page}

Karen Weiss, M.D.
Deputy Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Weiss
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