DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 1

NDA 20-839

Sanofi-Aventis
Attention: Nancy Barone Kribbs, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Kribbs:

Please refer to your correspondence dated October 12, 2006 (serial #658), requesting changes to our
October 15, 2001 Written Request for pediatric studies for Plavix (clopidogrel bisulfate).

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated October 15, 2001.

This Written Request contains a mixture of requirements (failure to fulfill these would result in denial of exclusivity) *and* advice. We have highlighted formal requirements to make this distinction clear.

STRATEGY

The requested data will provide guidance for the use of clopidogrel in the reduction of the incidence of thrombosis in children with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease. The following pediatric development plan will implement this goal:

1. Performance of a steady-state pharmacodynamic (PD) dose-ranging study in pediatric shunt patients who are in the age groups using the systemic to pulmonary artery shunt (neonates, age < 1 month, and infants/toddlers, age 1-24 months). This trial will provide for the selection of an appropriate dose for an efficacy and safety, placebo-controlled study in patients with systemic to pulmonary artery shunts.

2. Completion of an efficacy and safety placebo-controlled clopidogrel study in patients with systemic to pulmonary artery shunts.

3. Submission of a supplement summarizing all data available on the use of clopidogrel in patients undergoing systemic to pulmonary artery shunt placement, as well as a comprehensive safety evaluation of clopidogrel use in children. The safety evaluation in children receiving clopidogrel must include more than a summary of the published literature and include formal analyses of the available published and unpublished safety information. Examples of sources for unpublished safety information include institutions or organizations that systematically collect such data as part of their healthcare delivery to pediatric populations.

TRIAL DESIGN AND GENERAL CONSIDERATIONS
DOSE-RANGING PHARMACOKINETIC/PHARMACODYNAMIC STUDY

Pharmacodynamic data must be obtained from a dose-ranging study in pediatric patients at risk for thrombosis (including patients with therapeutic shunts of any kind) and who are in the same age range (neonates and infants/toddlers) as patients in the efficacy study. The goal of this study is to identify a dose providing steady state inhibition of platelet aggregation similar to that observed in adults taking clopidogrel (*i.e.*, 30 to 50% inhibition of ADP-induced platelet aggregation). The initial three doses used in the study must span a 10-fold range; however, if the lowest dose group provides little or no effect in the first few patients, modification of this dosing plan is acceptable in order to establish more rapidly which doses of clopidogrel have effects on platelet aggregation in the population. The results of this study will be the basis for the choice of the single dose to be used in the efficacy and safety study.

EFFICACY AND SAFETY STUDY

Dose levels for use in this study will be determined by a joint agreement between you and the Division, based upon the dose-response data in the pilot dose-ranging study.

This must be a placebo-controlled, double-blind clinical study in pediatric patients (neonates and infants/toddlers) receiving a systemic to pulmonary artery shunt for palliation of congenital heart disease. Patients must be randomized to clopidogrel (once per day at the determined dose) or to placebo following shunt placement, and then treated up to the time of the next surgical procedure for correction of their congenital heart disease. The study drug must be stopped in the following situations:

- Occurrence of any component of the primary efficacy endpoint
- The next surgical procedure is to be carried out
- Discontinuation is needed for management of an adverse event
- The parents or guardian request withdrawal
- The investigator decides that discontinuation is in the best interest of the patient

As there is no standardized care in this patient population, additional therapy must be in accordance with the usual practice of the institution (*i.e.* plus or minus concomitant aspirin).

The primary efficacy endpoint is the first occurrence of any component of the primary composite endpoint of:

- Death from any cause
- Shunt thrombosis requiring intervention, or
- Hospitalization for bi-directional Glenn procedure or any cardiac related intervention prior to 120 days of age following an event or a shunt narrowing considered thrombotic in nature.

STATISTICAL CONSIDERATIONS

Since there are closely related indications in adults, a claim in children would be supported by one study with an observed effect on the primary end point significant at $p < 0.05$. Your initial estimate of the sample size should be based upon sound estimates of the event rate and the usual statistical considerations.

Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. The study should use a population judged to be of adequate size, based on sound estimates of the effect size and usual statistical considerations. A relative risk reduction of 30% is acceptable for the power calculations. As there is no way to derive an assured event rate, the study must be event-driven; you must recruit until, based on the observed overall event rate, enough patients are enrolled to achieve the targeted number of events.

A full statistical analysis plan, including detailed plans for handling missing data, must be acceptable to the Division prior to first planned interim analysis.

EXTRAORDINARY RESULTS

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected, useful results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

RECRUITING

Both the dose ranging and the efficacy/safety studies should be performed in patients of both sexes in the pediatric age groups above, approximately evenly distributed among the relevant pediatric age groups to the extent possible given the patient population. The recruitment scheme should be designed to encourage broad enrollment with respect to gender and race.

DRUG INFORMATION

Use an age-appropriate formulation in the effectiveness study described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

GENERAL CONSIDERATIONS

Labeling that may result from the study(ies): Draft labeling must be submitted with appropriate sections of the label changed to incorporate the findings of the studies.

Format of reports to be submitted: You must submit 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 pediatric patients enrolled in the study(ies) should 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 should be used: Hispanic/Latino or Not Hispanic/Latino.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf and

referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/cder/guidance/6766fnl.pdf.

Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before July 31, 2011. 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.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to:

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 and 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, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
301.796.1130

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
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/

Robert Temple

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