DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839

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

Dear Dr. Kribbs:

Reference is made to your November 6, 2000 Proposed Pediatric Study Request for Plavix (clopidogrel bisulfate) submitted to IND 34,663.

To obtain needed pediatric information on clopidogrel 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 studies in pediatric patients described below.

STRATEGY

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

1. Performance of a steady state phamacodynamic (PD) dose-ranging study in pediatric shunt patients who are in the age groups using the Blalock-Taussig shunt (neonate and infant/toddler). This trial will provide for the selection of an appropriate dose for an efficacy and safety, placebo-controlled study in patients with Blalock-Taussig shunts.

2. Completion of an efficacy and safety placebo-controlled clopidogrel study in patients with Blalock-Taussig shunts.

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include more than a summary of the published literature and include formal analyses of the available published and unpublished safety information. Examples of sources for unpublished safety information include institutions or organizations that systematically collect such data as part of their healthcare delivery to pediatric populations.

PEDIATRIC AGE GROUPS

The five pediatric age groups that we refer to in this document are:

1. Neonates (age less than one month).
2. Infants and toddlers (age 1-24 months).
3. Pre-school children (age 2-6 years).
4. School-age children (age 6 to Tanner Stage 3).
5. Adolescents (Tanner Stage 3 to 16 years).

FORMULATION ISSUES

The studies described below should use an age-appropriate formulation of clopidogrel. The relative bioavailability of this formulation should be determined, compared with the marketed formulation of clopidogrel. Full study reports of any relative bioavailability studies should be submitted to the Agency. If an age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances, the use of a solid dosage form suspended in food or other formulations can be used, if it is standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

TRIAL DESIGN AND GENERAL CONSIDERATIONS

DOSE-RANGING PHARMACOKINETIC/PHARMACODYNAMIC STUDY

Pharmacodynamic data should be obtained from a dose-ranging study in pediatric patients with therapeutic shunts of any kind who are in the efficacy population age groups (neonates and infants/toddlers). 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 should provide a 10-fold difference between dose levels. 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 doses of clopidogrel with 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.

If the neonates and infants/toddlers have PD findings similar to those in adults, no further PD studies in the three older pediatric age groups (pre-school, school-age, and adolescent age) will be required. If additional studies are required, the single previously determined dose may be used for the older age groups, and the study may proceed in parallel to the planned efficacy and safety study in the neonates and infants/toddlers (see below). As the use of therapeutic shunts is rare in the pre-school, school age and adolescent-age populations, additional discussions about the numbers of patients required in these age groups may be necessary.

EFFICACY AND SAFETY STUDY

An efficacy and safety study that would be considered responsive to this request will be a placebo-controlled, double-blind clinical study in pediatric patients (neonates and infants/toddlers) receiving a modified Blalock-Taussig shunt for palliation of congenital heart disease. Patients should 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. Blood samples should be obtained in a sufficient number of subjects to analyze the population pharmacokinetic (PK) and PD profile for the chosen dose of clopidogrel, with PK based on the levels of the inactive metabolite of clopidogrel. Sparse sampling methodology can be used, provided sufficient samples are obtained at four times (one before peak serum concentrations, two following the peak, and one at or around the time of peak concentrations). Use of concomitant medications to prevent stent thrombosis should be left to the discretion of individual investigators.

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, but the study must be powered using objective clinical data demonstrating a realistic event rate for the primary endpoint, which is the combined incidence of any death, shunt thrombosis requiring intervention, and hospitalization for bi-directional Glenn procedure (prior to four months of age). The study should be designed with at least 80% power to detect a treatment effect at a conventional level of significance (p=0.05).

The study need not demonstrate that clopidogrel is effective at reducing the incidence of the primary endpoint when used in pediatric patients who undergo a modified Blalock-Taussig shunt placement, but it must be interpretable.

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. The recruitment scheme should be designed to encourage broad enrollment with respect to gender and race.

FORMAT OF REPORTS

Full study reports of the requested studies should be submitted as a supplement, including full analyses, assessments, and interpretations of the primary data.

LABELING CHANGES

The results of the completed studies may be used in the labeling of clopidogrel to add information allowing proper dosing for safe and effective use in the prevention of thrombosis in children with Blalock-Taussig shunts. A new indication will be approved only if the studies demonstrate safety and efficacy in the pediatric population studied that is distinct from the currently approved uses of clopidogrel.

TIMING OF SUBMISSION OF REPORTS

Reports on the above studies must be submitted to the Agency on or before 10 years from the date of the letter. Pediatric exclusivity only adds to the existing patent protection or exclusivity that has not expired at the time the study reports are submitted in response to this Written Request.

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.

Reports of the studies should be submitted as a new drug application or as a supplement to an approved NDA with the proposed labeling changes you believe would be 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. 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.

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.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, please call:

Ms. Colleen LoCicero
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Rachel Behrman, M.D., M.P.H
Deputy 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/

Rachel Behrman
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