DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-176 **WRITTEN REQUEST #2**

Sankyo Pharma Development
Attention: Jean Lyons
Associate Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Ms. Lyons:

Reference is made to your Proposed Pediatric Study Request for colesevelam hydrochloride submitted on April 30, 2004, to NDA 21-176.

To obtain needed pediatric information on colesevelam hydrochloride, 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 28-week study in pediatric patients (males and females) with heterozygous familial hypercholesterolemia (heFH) that evaluates the effect of colesevelam hydrochloride on LDL-C. The study should include the following treatment periods:

  Period 1 is a 4-week, randomized, placebo-controlled, parallel-group, dose-ranging study with the following treatment groups:
  - placebo (n=40)
  - colesevelam hydrochloride low dose (n=80)
  - colesevelam hydrochloride high dose (n=80)

  Period 2 is a 6-week, active-control period. Patients from Period 1 who were receiving colesevelam hydrochloride high dose will be randomized to receive either colesevelam hydrochloride high dose in combination with a statin that is FDA approved for this age range, or continue on the high dose of colesevelam hydrochloride alone. Patients from Period 1 who were receiving colesevelam hydrochloride low dose will be randomized to receive either colesevelam hydrochloride low dose in combination with an FDA-approved statin or continue on the low dose of colesevelam hydrochloride alone. Patients from Period 1 who were receiving placebo will be treated with an FDA-approved statin. The statin dose will be the same in all treatment groups. In total, there will be 5 treatment groups in this period:
  - colesevelam hydrochloride low dose (n=40)
  - colesevelem hydrochloride high dose (n=40)

- colesevelam hydrochloride low dose in combination with an FDA-approved statin (n=40)
- colesevelam hydrochloride high dose in combination with an FDA-approved statin (n=40)
- FDA-approved statin monotherapy (n=40)

Period 3 is an 18-week, extension period where statins may be initiated or increased in dose for patients not adequately treated during Period 2.

Enrollment should target equal numbers of male and female patients in this study.

Periods 1 and 2
Approximately 200 patients should complete these two phases of the study.

Period 3
Approximately 120 patients should complete this phase of the study.

- ***Indications to be studied:***

To characterize the safety and to assess the effect of colesevelam hydrochloride monotherapy on plasma lipids in pediatric patients with heFH.

To characterize the safety and to assess the effect of combination therapy of colesevelam hydrochloride and an FDA-approved HMG-CoA reductase inhibitor on plasma lipids in pediatric patients with heFH.

- ***Age group in which study will be performed*:**

Male and female pediatric patients aged 10 through 16 years, inclusive, who are at least Tanner stage 2.

Female patients must be at least 1 year post-menarchal.

- ***Study endpoints:***

The primary efficacy variable in Periods 1 and 2 will be the percent change in LDL-cholesterol level. Secondary efficacy variables will be the percent change in levels of total-C, HDL-C, and TG.

- ***Drug information:***
  - ***Dosage form****:* Marketed 625-mg tablets.
  - ***Route of administration:*** Oral.
  - ***Regimen:*** Low dose 2 tablets per day for body weights < 50 kg
    3 tablets per day for body weights ≥ 50 kg

    High dose 4 tablets per day for body weights < 50 kg
    6 tablets per day for body weights ≥ 50 kg

- Use an age-appropriate formulation in the study described above. Any unapproved formulation will need to be supported by study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency.

- ***Drug-specific safety concerns*:**

Effects on the gastrointestinal system (i.e., constipation, dyspepsia).

Effects on vitamin K or other fat-soluble vitamin deficiencies as monitored by PT/PTT and vitamin A and E levels.

Effects on liver and muscle as monitored by serum transaminase and creatinine kinase levels.

Effects on growth and sexual maturation as assessed by stadiometry and Tanner staging.

- ***Statistical information, including power of study and statistical assessments:***

Conduct two primary treatment comparisons of Period 1 data:
(1) low-dose colesevelam versus placebo
(2) high-dose colesevelam versus placebo

Conduct two primary treatment comparisons of Period 2 data:
(3) statin in combination with low-dose colesevelam versus statin alone
(4) statin in combination with high-dose colesevelam versus statin alone

All other treatment comparisons will be considered secondary.

The primary efficacy variable in both Periods is the percent change in LDL-C from baseline (day 1 of Period 1).

Each primary treatment comparison will test the null hypothesis that the mean percent changes from baseline in LDL-C in the two groups are equal. Null hypotheses should be tested using an ANOVA or ANCOVA with appropriate factors in the model. If assumptions for the individual parametric tests are not satisfied, appropriate transformations of the data or nonparametric methods may be performed.

The primary analysis population for the primary treatment comparisons of Period 1 data will be the intent-to-treat population consisting of all randomized patients with a baseline and at least one on-treatment LDL-C measurement. Data for patients without Week 4 evaluations will consist of the last available observation (LOCF).

The primary analysis population for the primary treatment comparisons of Period 2 data will be the intent-to-treat population consisting of all randomized patients with a baseline and at least one on-treatment LDL-C measurement. Data for patients without Week 10 evaluations will consist of the last available observation from Periods 1 and 2. A second LOCF analysis of Period 2 data should be performed excluding data carried forward from Period 1.

Descriptive statistics should be presented for LDL-C during Period 3 and for secondary plasma lipids at each visit.

- ***Labeling that may result from the study*:** Appropriate sections of the label may be changed to incorporate the findings of the study.
- ***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. Include other information as appropriate. All pediatric patients enrolled in the study must 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 must be used: Hispanic/Latino or Not Hispanic/Latino.
- ***Timeframe for submitting reports of the study:*** Reports of the above studies must be submitted to the Agency on or before January 1, 2008. 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.
- 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. Please 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 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, please 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, call Valerie Jimenez, Project Manager, at 827-9090.

Sincerely,

Robert J. Meyer, M. D.
Director
Office of Drug Evaluation II
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 Meyer

8/31/04 09:48:39 AM