DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND (b) (4)
NDA 21-141
NDA 21-176

WRITTEN REQUEST
Amendment #3

Daiichi-Sankyo
Attention: Sandra Smith
Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Ms. Smith:

Please refer to your correspondences to IND (b) (4) dated September 28 and November 29, 2006, requesting changes to FDA's Written Request for pediatric studies for colesevelam hydrochloride.

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 August 31, 2004, as amended January 19 and March 28, 2006, with the revised sections highlighted in **bold** font.

- *Type of study(ies)*:

A 30-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 period in which heFH patients are entering on a stabilized pediatric approved statin dose (atorvastatin, simvastatin, pravastatin, lovastatin) or stabilized on a low cholesterol diet and statin naïve.

- Period 2 is an 8-week period in which sufficient patients from Period 1 are randomized equally to one of 3 parallel treatment groups to achieve at least **132** evaluable patients:

  - placebo dose
  - colesevelam HCl low dose (1875 mg, 3 tablets)
  - colesevelem HCl high dose (3750 mg, 6 tablets)

  Randomization will be stratified by statin use (any, none) in period 1. All patients receiving statins will not have their dosage changed during Period 2. Statin-naïve patients will receive only assigned study drug during Period 2.

- Period 3 is an 18-week, open-label, long-term extension period where all patients are given high-dose colesevelam HCl (3750 mg). Patients stabilized on statins may then have their statin doses incremented per label. Patients who are naïve to statin therapy will additionally be offered a pediatric approved statin therapy per investigator discretion. Treatment goal for all heFH patients is LDL-C < 110 mg/dL by incrementing statin dose per label.

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

Period 3: Approximately **100** patients should complete this phase of the study.

- *Indication to be studied*

To characterize the safety and lipid-lowering efficacy (LDL-C) of colesevelam HCl administered to pediatric patients diagnosed with heFH, who are receiving a stable dose of a statin or are treatment naïve to statin therapy.

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

Male and female pediatric patients aged 10 through 17 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 will be the percent change in LDL-cholesterol level from study baseline (Day 1 of Period 2) to Week 8 (end of Period 2). Secondary efficacy variables will be the percent change in LDL-C from Period 3 baseline to Week 26 and from study baseline (Day 1) to Week 26.

Additional secondary efficacy variables are the percent changes in total-C, HDL-C, Apo A1, Apo B, and TG from study baseline (Day 1) to Week 8 of Period 2; and from Period 3 baseline to Week 26.

- *Drug information*

  - *Dosage form* Marketed 625-mg tablets
  - *Route of administration* Oral
  - *Regimen*

    Low dose: 3 tablets per day (no weight stratification)

High dose: 6 tablets per day (no weight stratification)

Use an age-appropriate formulation in the studies 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.

- *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 with respect to the primary efficacy variable percent change in LDL-C from Day 1 of Period 2 (study baseline) to Week 8 (end of Period 2):

1. Comparison will first be performed between the high-dose colesevelam group (3750 mg) and the placebo group. If the null hypothesis is rejected in favor of the high-dose colesevelam group,

   then:

2. A comparison between the low-dose colesevelam group (1850 mg) and the placebo group will be performed.

Otherwise, no comparison will be performed between the low-dose colesevelam HCl group and the placebo group.

All other treatment comparisons will be considered secondary. The analyses of the secondary efficacy variables are similar to that used for the primary efficacy variable.

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 a parametric ANOVA (with treatment and randomization stratification variable [statin use in Period 1] as factors) or ANCOVA (with treatment and randomization stratification variable [statin use in Period 1] as factors and baseline LDL-C value as a covariate). If assumptions for both parametric tests are not valid, nonparametric ANCOVA may be performed. Secondary analyses should be performed to assess the consistency of treatment effects with and without statins.

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 post-baseline lipid measurement. Data for patients without Week 8 lipid measurements will be imputed using the Last Observation Carried Forward (LOCF).

Descriptive statistics will be presented for LDL-C and secondary efficacy variables when measured at each visit during Period 3. Descriptive statistics should also be presented for height velocity and sexual maturation at the end of Period 3.

- *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. 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.

- *Timeframe for submitting reports of the studies*

Reports of the above studies must be submitted to the Agency on or before **October 1, 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.

Submit reports of the studies as a new drug application (NDA) or 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 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 Kati Johnson, Project Manager, at 301-796-1234.

Sincerely,

{See appended electronic signature page}

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

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