DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 58,627

GlaxoSmithKline
Attention: Anne Stokely, M.S.P.H.
Director, Antiviral/Anti-infective Regulatory Affairs
Five Moore Drive
Research Triangle Park
North Carolina 27709

Dear Ms. Stokely:

Please refer to your correspondence dated June 10, 2002, requesting changes to FDA's December 26, 2001, Written Request for pediatric studies for GW433908 for the treatment of HIV infection.

We 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 supercedes the Written Request dated December 26, 2001.

Reports of the studies that meet the terms of this Written Request must be submitted to the Agency on or before August 2006, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Type of studies:

Multiple-dose pharmacokinetic and safety study of GW433908 alone and GW433908 in combination with low-dose ritonavir in HIV-infected pediatric patients.

The objective of these studies will be to determine the pharmacokinetic and safety profile of GW433908 across the age range studied, identify an appropriate dose for use in HIV-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment. Studies that do not define the therapeutic dose in pediatric patients in all studied age groups will be interpreted by the Division/FDA as non-responsive to this Written Request.

Indication to be studied:

Treatment of HIV infection in pediatric patients.

Age group in which studies will be performed:

HIV infected pediatric patients from four weeks to adolescence.

Drug Information

Dosage form: 465 or 700 mg tablets, and age appropriate-formulation (s).

The studies described above should use an age-appropriate formulation of GW433908**.** The relative bioavailability of this formulation should be determined and compared with the marketed formulation of GW433908. 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 other formulations can be used, if they are standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

- Route of administration: oral
- Regimen: to be determined by development program

Drug specific safety concerns:

- *Rash, including Stevens-Johnson syndrome*
- *Gastrointestinal symptoms*
- *Elevated liver transaminase levels*
- *Elevated trigylcerides*
- *Metabolic disorders such as hyperglycemia, hyperlipidemia, abnormal fat redistribution.*

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address.

The safety of GW433908 must be studied in an adequate number of pediatric patients to characterize adverse events across the age range.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients. A minimum number of pediatric patients (as stated below) should complete the pharmacokinetic study(ies) conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

Four weeks to < six months: 8 patients
Six months to < two years: 6 patients
Two years to < six years: 12 patients
Six years to < 12 years: 8 patients
12 years to < 17 years: 6 patients

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients should be generally well distributed across the age range studied.

Study endpoints:

Pharmacokinetics
Pharmacokinetic parameters such as: Cmax, Cmin, Tmax, t ½, AUC, and apparent oral clearance

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of six months at the recommended dose. In addition, please also submit plans for long-term safety monitoring in HIV-infected pediatric patients who have received GW433908.

Safety data should be collected on approximately 100 patients.

Activity

Assessment of changes in plasma HIV RNA levels and in CD4 cell counts (in HIV-infected pediatric patients)

Resistance

Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving GW433908, particularly from those who experience loss of virologic response.

Labeling that may result from the study(ies):

Information regarding dosing, safety and activity in the HIV-infected pediatric population.

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 of the representation of pediatric patients of ethnic and racial minorities.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before August 2006. 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. 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 new drug application 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.

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, please call Destry M. Sillivan, Regulatory Project Manager, at 301-827-2335.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D.
Director
Office of Drug Evaluation IV
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/

Mark Goldberger
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