DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 43,468
NDA 21-071

GlaxoSmithKline
Attention: Sharon Shapowal, R.Ph.
Director, U.S. Regulatory Affairs
P.O. Box 7929
Philadelphia, PA 19101-7929

WRITTEN REQUEST
Amendment # 1

Dear Ms. Shapowal:

Reference is made to your correspondence dated March 31 and July 31, 2000, May 10, and and February 11, 2002, to IND 43,468, requesting changes to FDA's February 1, 2000, Written Request for pediatric studies for rosiglitazone maleate.

We have reviewed your proposed changes to your protocol entitled, "A 24-week Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Rosiglitazone When Administered to Pediatric Patients with Type 2 Diabetes Mellitus" (Protocol: Rosiglitazone / 207 Phase III), and are amending below the listed sections to the Written Request. We note that additional changes from your May 10, 2001, submission included Asian/Pacific region investigators, and the distribution of glucose meters at the beginning of the run-in period, rather than at randomization. All other terms stated in our Written Request issued on February 1, 2000, remain the same.

Additional comments follow the amendment to the Written Request. These comments are not part of the Written Request.

Study Design:

Study 1: A single-dose pharmacokinetic study in which a 4.0 mg dose of rosiglitazone is administered with breakfast. Alternatively, a population pharmacokinetic study with sparse sampling approach may be conducted in a subset(s) of patients in Study 2 during rosiglitazone monotherapy.

Study 2: A double-blind, randomized, active-controlled clinical trial of 24-weeks duration in pediatric patients with type 2 diabetes not adequately controlled on diet and exercise alone. The study treatment should be titrated at 8 weeks as necessary to achieve target fasting plasma glucose (FPG) < 126 mg/dL. The dose should remain constant for at least the last 8 weeks of the study (weeks 16-24).

Age group in which study will be performed:

Patients will be 8 to ≤17 years of age.

Number of patients to be studied:

At least 75 completers per arm.

Entry Criteria;

Study 1: Attempt to include equal numbers of patients in the ≤12 and 13 to ≤17 year old age groups, with an equal number of patients of each gender in each age group.

Study 2: Patients with a clinical diagnosis of type 2 diabetes with HbA1c values between 7.1 to 10%, and post-Sustacal C-peptide levels ≥ 1.5 ng/dL, are to be randomized in a 1:1 ratio to receive either Avandia or metformin. Glutamic acid decarboxylase (GAD) and 1CA512 autoantibodies must be shown to be negative to exclude a diagnosis of type 1 diabetes. Patients will be excluded who have renal disease or renal dysfunction (serum creatinine ≥1 mg/dL or abnormal creatinine clearance); congestive heart failure; clinical or laboratory evidence of hepatic disease; acute or chronic metabolic acidosis. All subjects will receive intensive training in the principles of diet and exercise therapy. Patients will be recruited from those who have and those who have not previously received an oral hypoglycemic agent; however, every attempt should be made to enroll naïve patients.

Statistical Information, including:

Study 1: Standard summary statistics and analysis of pharmacokinetic data.

Study 2: Treatment group comparisons for change from baseline in HbA1c will be made using an analysis of covariance (ANCOVA) model with baseline as covariate. The analysis will be conducted with the type I error rate controlled at the two-sided 0.05 level. The treatment difference in mean change from baseline in HbA1c will also be assessed by confidence interval methods using adjusted means and the associated standard error from the ANCOVA model. To assess non-inferiority of the test drug compared to control, a non-inferiority margin of –0.4% in HbA1c should be applied. The ultimate selection of the non-inferiority margin is a review issue based on the data available at the time of evaluation.

Analyses of data from both the intent-to-treat (ITT) population and the completers will be performed to ascertain if dropouts biased the ITT results. The ITT population will include all randomized patients who have baseline data and any post-baseline data.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before September 30, 2003. Please keep in mind that pediatric exclusivity only extends patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Reports of the studies that meet the terms of the Written Request dated September 21, 1999, as amended by this letter must be submitted to the Agency on or before September 30, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Additional Comments:

Criteria for withdrawal:

Because of hyperglycemia occurring during the treatment phase, criteria for withdrawal should be stricter than the two values of FPG ≥225 mg/dL. Proposed withdrawal (or rescue) criteria used should be FPG of ≥230 mg/dL at 2 weeks; ≥180 mg/dL at 4 weeks; ≥140 mg/dL at 6 weeks and beyond. Transaminases (ALT or AST) that are 3x the upper limit of normal should be repeated. If transaminase elevations persist, patients should be withdrawn from the trial.

You should also develop withdrawal criteria for other abnormal laboratory values: (e.g., creatinine, blood urea nitrogen [BUN], hematocrit, hemoglobin).

Anemia:

You have proposed enrollment of children with Hgb > 10 (females) or Hgb >11 (males). Since rosiglitazone treatment may be associated with anemia, we suggest children with normal hematologic profiles be enrolled.

Cardiac disease:

Children with underlying cardiac disease (e.g., congenital anomaly) should be excluded.

Hypertension:

The exclusion criterion of 160/110 mm Hg as stated in the protocol is too high. Children with blood pressure normal for age and sex should be enrolled.

Body weight and height:

Body weight and height should be measured at all visits; shortness of breath and peripheral edema should also be assessed. Patients with edema or excess weight gain should be withdrawn from further participation. Please provide criteria for edema and weight gain at which escape or discontinuation from the study should occur. Diuretic use, if any, should be documented.

Serum βHCG:

Serum βHCG should be measured at 12 weeks, in addition to baseline and 24 weeks.

Informed consent:

> Though the consent form states that a placebo will be administered for part of the study, it does not state that the patients may become hyperglycemic and symptomatic during this time, particularly if they have been withdrawn from other pharmacologic therapy. This statement should be included in the consent form.

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. Please 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 NDA 21-071 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 to the pediatric population.

If you have any questions, contact Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Sandra Kweder, M.D.
Acting 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/

Sandra L. Kweder

5/24/02 11:56:56 AM