DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-071
IND 43,468

S.B. Pharmco Puerto Rico, Inc.
d/b/a/ GlaxoSmithKline
Attention: Sharon W. Shapowal, R.Ph.
P.O. Box 7929
Philadelphia, PA 19101-7929

WRITTEN REQUEST #2

Dear Ms. Shapowal:

Reference is made to your Proposed Pediatric Study Request submitted on May 2, 2003, to IND 43,468, for Avandia® (rosiglitazone maleate) Tablets.

To obtain needed pediatric information on rosiglitazone, 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 studies:

Type of Study:
Study 1: A single-dose pharmacokinetic study or, alternatively, a population pharmacokinetic study in pediatric patients with type 2 diabetes.

Study 2: A clinical trial of 24-weeks duration comparing rosiglitazone maleate monotherapy versus metformin monotherapy in pediatric patients with type 2 diabetes.

Indication to be studied (objective/rationale):
Treatment of hyperglycemia in pediatric patients with type 2 diabetes whose hyperglycemia is not adequately controlled on a regimen of diet and exercise alone.

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:
Study 1: For a single dose pharmacokinetic study, at least 12 patients (preferably 6 males and 6 females) are to be studied. If the study design is a population pharmacokinetic study of a subset of patients from the Avandia arm of Study 2, 3 – 4 blood samples should be obtained from each of at least 30 patients. For a population pharmacokinetic study, it is recommended that blood samples be collected randomly over a 12-hour dosing period.

Study 2: 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.

Study endpoints and timing of assessments, including primary efficacy endpoints:
Study 1: Pharmacokinetic parameters such as AUC, Cmax, Tmax, CL/F, Vss/F, and $t_{1/2}$ will be determined. If possible, the effect of demographic covariates (e.g., age, gender, and body weight) on pharmacokinetic parameters will be assessed.

Study 2: The primary efficacy measure will be the change from baseline in HbA1c at week 24. Secondary efficacy measures will include FBG. Safety assessments will include vital signs, adverse events, body weight, and episodes of hypoglycemia.

Drug information:
- **Dosage form:** Tablets
- **Route of administration:** Oral
- **Regimen:** Study 2 Avandia: initially 2 mg twice a day titrated to 4 mg twice a day at 12 weeks. Metformin: initially 500 mg twice a day titrated to 1000 mg twice a day at 12 weeks.
- **Formulation:** Same as marketed.

Drug-specific safety concerns:
Changes in body weight increments and episodes of hypoglycemia.

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.

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.

Timeframe for submitting reports of the above studies: Reports of the above studies must be submitted to the Agency on or before September 30, 2004. 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 a 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. 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.

Submit reports of the studies as a supplement to NDA 21-071 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.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to NDA 21-071. 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.

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.

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

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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