HFD-104

NDA 21-071

FEB 1 - 2000

SmithKline Beecham Pharmaceuticals
Attention: Sharon W. Shapowal, R.Ph.
Director, Avandia U.S. Regulatory Affairs
One Franklin Plaza, Mailcode: UP4305
Philadelphia, PA 19102

Dear Ms. Shapowal:

Reference is made to your Proposed Pediatric Study Request dated September 21, 1999, for Avandia (rosiglitazone) Tablets, submitted to IND 43,468.

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:

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 Avandia 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 12 weeks as necessary to achieve a target FPG < 140 mg/dL.

A sequential, escalating dose titration schedule of 2 mg twice a day initially and 4 mg twice a day at week 12 for Avandia, and 500 mg twice a day initially and 1000 mg twice a day at week 12 for metformin is recommended. At your discretion, a third arm of Avandia plus metformin can be added.

Age group in which study will be performed:

Age range will be 8 to 16 years of age inclusive with at least 25% of patients in both treatment groups in the 8 – 10 year age range.

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: 75 patients in each arm.

Entry Criteria:

Study 1: Attempt to include equal numbers of patients in the 8 – 12 and 13 – 16 year age groups, and an equal number of patients for each gender in each age group.

Study 2: Patients with a clinical diagnosis of type 2 diabetes with HbA1c values between 7.1 and 10% and post-Sustacal C-peptide levels $\geq$ 1.5 ng/dL are to be randomized in a 1:1 ratio to receive either Avandia or metformin. GAD and 1CA512 autoantibodies must be shown to be negative to exclude a diagnosis of type 1 diabetes. Patients must have a serum creatinine $<$ 1.0 dL/mL or be shown to have a normal creatinine clearance. All subjects will receive intensive training in the principles of diet and exercise therapy. Patients will be recruited from those who have not previously received an oral hypoglycemic agent.

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.

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.

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted:

Full study reports or analyses not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation, and with accompanying computer-based clinical and safety data listings.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before April 30, 2002. 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.

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 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 you 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 the 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 contact Ms. Jena Weber, Regulatory Health Project Manager, at (301) 827-6422.

Sincerely yours.

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc:
IND 43,468
NDA 21-071
HFD-510/division file (2)
HFD-510/Dorloff/Smalozowski/Rmisbin/Jwei/HYAhn/Jwang/Tsahlroot
HFD-102/JJenkins/LRipper
HFD-600/OGD
HFD-2/Mlumpkin
HFD-104/Dmurphy
HFD-002/Tcrescenzi

Drafted by JMW 1/31/2000
Cc:Rmisbin 1/31/Smalozowski 1/20/ SJWang 1/6/Tsahlroot 1/19/ Jwei 1/19/ HYAhn 1/7/00/Lripper 1/31/Jjenkins 2/1/00

Final: 02/01/2000 2/1/00

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PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)