

NDA 21-071

SmithKline Beecham Pharmaceuticals
Attention: G. Clare Kahn, Ph.D.
Group Director, U.S. Regulatory Affairs
P.O. Box 7929
Philadelphia, PA 19101

Dear Dr. Kahn:

Please refer to your new drug application (NDA) dated November 25, 1998, received November 25, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandia™ (rosiglitazone maleate tablets), 2, 4, and 8 mg.

We acknowledge receipt of your submissions dated January 28, February 4, 18, and 22, March 2, 18, and 31, April 2, 7, 12, 13, 20, and 28, and May 20, 21, 24, and 25, 1999.

This new drug application provides for the use of Avandia (rosiglitazone maleate tablets) as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus as monotherapy or in combination with metformin.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician labeling submitted May 25, 1999, immediate container and carton labels submitted May 21, 1999, and patient trial kit, 2 mg and 4 mg, submitted April 28, 1999. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-071." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated May 25, 1999, to conduct a long-term (4-year) safety and efficacy study (titled "ADOPT" study) of Avandia monotherapy compared to metformin or glipizide in patients with drug-naive, recent-onset (less than 2 years) type 2 diabetes mellitus. The study will assess maintenance/restoration of pancreatic beta-cell insulin secretion and long-term safety (incidence of ALT elevations, cardiovascular and hematologic events, changes in body weight and serum lipids). The final draft protocol will be submitted by September 1, 1999. The study will be initiated within 3 months after mutual agreement on the protocol design but not later than March 1, 2000.

The protocol, data, and final report should be submitted to your IND for this product with a copy of the cover letter sent to this NDA. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary in your annual reports to this NDA. The status summary should include the number of patients entered, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment should be clearly designated "Phase 4 Commitment."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. We are deferring submission of your pediatric studies until December 2, 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details.

If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit

a pediatric drug development plan] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Validation of the regulatory methods has not yet been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

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