DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-297

GlaxoSmithKline
Attention: Ms. Catherine K. Clark.
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101

Dear Ms. Clark:

Reference is made to the Pediatric Written Requests for studies of carvedilol issued December 23, 1998, May 7, 1999 and October 3, 2000 and reissued July 2, 2002 following the enactment of the Best Pharmaceuticals for Children Act, to your letter of June 14, 2002 requesting an amendment to the Written Request, and to a teleconference February 11, 2003 with the Division of Cardio-Renal Drug Products.

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), to obtain needed pediatric information for carvedilol. This Written Request supercedes the requests issued December 23, 1998, May 7, 1999, October 3, 2000 and July 2, 2002. We request that you submit information from trials in pediatric patients as described below. Some of the changes include:

- Specific requirements are amended for the age distribution.
- Specific criteria are set for the interpretability of unsuccessful studies.
- The date for submission of a final report has been extended.

Strategy

The requested data will provide guidance for the use of carvedilol to treat heart failure in pediatric patients. These data will be derived from

- an outcome trial in which carvedilol and placebo are added to standard therapy in pediatric patients with heart failure, and
- safety data derived from a controlled trial and a 1-year open treatment phase following the trial, with a summary of all available information on the safety of the drug in pediatric patients with heart failure. The safety evaluation in children must include a summary of the published literature and formal analyses of published and unpublished data. Unpublished data may be obtainable from organizations participating in healthcare delivery to the pediatric population.

Pediatric Subgroups

Age groups

Subjects who are Tanner Stage 3 to <18 years may comprise up to 50% of enrollment. The remainder must be less than Tanner Stage 3.

Racial groups

Your recruitment scheme should be designed to assure the enrollment of a mixture of black and non-black subjects.

Formulation Issues

Formulations must be well characterized and appropriate to the age and clinical setting. Any unapproved formulation will need to be supported by a study of the relative bioavailability of carvedilol; these studies may be conducted in adults. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and you will need to obtain an agreement with the Agency regarding the adequacy of the formulation you use. Full study reports of any relative bioavailability studies must be submitted to the Agency.

Outcome Trial

Trial design

The trial must be at least a 6-month, randomized, double-blind, parallel comparison of carvedilol and placebo in a population judged to be of adequate size based on realistic estimates of effect size and usual statistical calculations. The most straightforward trial would be one in which each subject is randomized to placebo or to the maximally tolerated dose of carvedilol, titrated up from a low starting dose. The trial should not screen subjects for the ability to tolerate beta-blockers prior to randomization, but should randomize all candidates. The trial is to be analyzed by looking for a treatment-related reduction in end point events (e.g., death or cause-specific hospitalization) or other indications of clinical benefit (e.g., NYHA class[1] or growth) in the entire randomized population.

Other than with regard to the use of beta-blockers, background therapy should conform to the local standards of care.

There should be an independent data monitoring committee that assess ongoing results. Stopping rules for benefit and adverse events should be developed.

Recruiting

Subjects recruited for the trial should be diagnosed with heart failure according to the standards of local practice. They must not be recruited if other interventions likely to affect heart failure (e.g., repair of cardiac anomalies or transplant) are likely to occur during the course of the trial. Prior treatment with carvedilol or other specific therapy should be neither required nor disqualifying.

Statistical considerations

The trial must be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance. Submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes.

Interpretability

A successful study ($p<0.05$ for its pre-specified primary end point analysis) is clearly interpretable. An unsuccessful study will be considered interpretable if it demonstrates that the study was powered to find a "clinically meaningful" treatment benefit (change from baseline and placebo).

The latter requires you to show by a post-hoc power analysis based on the observed variability, that if the true treatment effect were "clinically meaningful", the 95% confidence interval would have excluded zero treatment effect with ≥90% power. You may wish to obtain an estimate of variability from a preliminary study, or you may obtain a penalty-free estimate of variability from a pooled interim analysis (without unblinding) and then follow a pre-specified rule to adjust the sample size.

For the purpose of satisfying the interpretability criteria of this Written Request, a clinically meaningful treatment benefit is considered to be a 10% effect on outcome events or a 20% effect on symptoms or global assessment score.

An unsuccessful and uninterpretable result will be considered responsive to the Written Request if the study enrolls a minimum of 150 subjects and was otherwise designed and conducted according to sound clinical research principles.

Any other unsuccessful result will be considered not interpretable. A study that is not interpretable will be considered not responsive to the Written Request.

---

1 A categorical test like NYHA class or global response as improved, unchanged or worsened can, if there are more than two categorical values, have outcomes that distinguish between groups but that are, nonetheless, not clearly evidence of benefit. For this reason, if the primary end point has 3 or more categorical response values, the primary analysis and interpretability criteria must be based on a prospectively specified binary comparison, e.g. lumping NYHA class to I+II vs. III+IV or global response to Improved+Unchanged vs. Worsened.

Long-term safety

Patients in the trial(s) of clinical efficacy should be enrolled in an open-label follow-on study with safety (adverse events), growth (change in head circumference[2], weight, length or height), and development (milestones, school performance, neurocognitive testing) assessed at baseline and at one year.

Pharmacokinetic Trials

Pharmacokinetic data must be obtained over the range of doses studied for effectiveness. Patients must have grossly normal metabolic function. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters.

Data must be collected with respect to carvedilol and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected must provide estimates of the exposure (AUC), half-life, oral apparent clearance, volume of distribution, C_{max} , and t_{max} in pediatric subjects of the various age groups.

Labeling Changes

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

Reporting

Full study reports of the requested trials, including full analysis, assessment, and interpretation, must be submitted in the usual format. As an alternative, you may submit an abbreviated study report along with all data in electronic form, with a case report form annotated with the names of the SAS variables used for each blank on the form.

Reports of the above studies must be submitted to the Agency on or before September 6, 2006. Remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

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. You should identify any discrepancies between your proposed protocol and the Written Request. If there are differences, it is your responsibility to seek an amendment to the Written Request or to seek a Written Agreement.

Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark such a 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 must be submitted 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, 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. Also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

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, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request must be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the

[2] *Up to age of 3 years.*

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, please contact:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

Rachel Behrman, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation I
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/

Rachel Behrman

5/28/03 02:35:38 PM