DEPARTMENT OF HEALTH & HUMAN SERVICES

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Amended

Food and Drug Administration
Rockville MD 20857

Four Years from the Date of this Letter OCT 3 2004

NDA 20-297
IND 27,114

OCT 3 2000

SmithKline Beecham Pharmaceuticals
Attention: Ms. Catherine Clark
1250 S Collegeville Rd
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Clark:

Reference is made to our May 7, 1999 Written Request for pediatric studies for Coreg **(carvedilol).** Please note that the following Written Request supercedes that of May 7, 1999, which is no longer valid.

To obtain needed pediatric information on carvedilol, 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 trials in pediatric patients described below.

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

- outcome trials in which carvedilol and placebo are each added to standard therapy in pediatric patients with heart failure; and
- safety data derived from the controlled trial and an open treatment phase following the trial, with a summary of all available information on the safety of the drug in pediatric patients.

Pediatric Subgroups

Age groups

The five pediatric age groups to which we refer in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1-- 24 months),
- pre-school children (age 2-- 6 years),
- school-age children (age 6 --Tanner Stage 3), and
- adolescents (Tanner Stage 3-- 16 years).

With respect to effectiveness, studies of heart failure drugs should be focused on prepubertal children. Both school age and pre-school patients should be studied. If you prefer, the school age children could be studied first. The pre-school group should be widened to include neonates, infants and toddlers. We are not requesting studies in adolescents. Although this group could differ from younger or older patients in its response, we believe the studies in younger patients, together with data on adults, will provide a sufficient basis for treatment of this group.

Racial groups

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

Formulation Issues

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if it were standardized, palatable, and with bioavailability shown in adults to be similar to the marketed product, or different from the marketed product in a well-defined way.

Controlled Outcome Trial

Trial Design

The trial should be a 6-month randomized, double-blind, parallel comparison of carvedilol and placebo in a population judged to be of adequate size on the basis of realistic estimates of effect size and the usual statistical calculations. The most straightforward trial would be one in which each patient is randomized to placebo or to the maximally tolerated dose of carvedilol, titrated up from a low starting dose. The trial should not screen people for ability to tolerate beta blockers prior to randomization but should randomize all candidates. The trial would be analyzed by looking for a treatment-related reduction in end point events (death or cause-specific hospitalization), and other indications of benefit (NYHA class, 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 assesses ongoing results; stopping rules for benefit and adverse effects should be developed.

Recruiting

Patients recruited for the trial should be diagnosed with heart failure according to the standards of local practice. They should 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 expected course of the trial. Prior treatment with carvedilol or other therapy should be neither required nor disqualifying.

Duration

The study period should generally be of six months duration.

Statistical considerations

The trial should be designed with at least 80% power to detect a treatment effect of conventional (P= 0.05) statistical significance. Please 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.

Pharmacokinetic Trials

Data should 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 should provide estimates of the bioavailability (AUC), half-life, C_{max}, and t_{max} in pediatric subjects of the various age groups. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

Some or all of the pharmacokinetic data may be obtained from patients in the effectiveness trial or from safety studies, using traditional or sparse sampling to estimate pharmacokinetic parameters.

Format of Reports

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should 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.

Labeling Changes

The results of the completed studies may be used in the labeling of your drug products to add information allowing proper dosing for the safe and effective use for the treatment of heart failure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your products are approved.

Timing of Submission of Reports

Reports of the above studies must be submitted to the Agency on or before four years from the date of this letter. Please remember that pediatric exclusivity only adds 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.

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. To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. 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 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 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:

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, please contact:

Ms. Zelda McDonald
Regulatory Heath Project Manager
(301) 594-5333

Sincerely yours,

Rachel E. Behrman, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA/IND
HFD-110/division file
HFD-101/Office Director
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-104/TCrescenzi
HFD-110/ZMcDonald

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PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)