HFD-104
Murphy

MAY 20 1999

NDA 20-236

GlaxoWellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Ramona Krailler, Ph.D.
Director
Regulatory Affairs

Dear Dr. Krailler:

Reference is made to your Proposed Pediatric Study Request submitted on February 19, 1999, to NDA 20-236 for salmeterol xinafoate inhalation aerosol.

To obtain needed pediatric information on salmeterol xinafoate, 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 studies:
Study 1: Dose-ranging safety of salmeterol xinafoate for treatment of asthma in children between the ages of 2 years and <4 years.
Study 2: Efficacy and safety of salmeterol xinafoate for treatment of asthma in children between the ages of 2 years and <4 years.
Study 3: Dose-ranging safety of salmeterol xinafoate for treatment of asthma in children between the ages of 6 months and <2 years.
Study 4: Efficacy and safety of salmeterol xinafoate for treatment of asthma in children between the ages of 6 months and <2 years.

Objective/Rationale:
Studies 1 and 3: Characterize the dose-response on safety endpoints among different doses of salmeterol inhalation aerosol delivered with two different spacers in children with asthma between the ages of 2 years and <4 years, and 6 months and <2 years.
Studies 2 and 4: Assess the efficacy and safety of salmeterol inhalation aerosol delivered with two different spacers in children with asthma between the ages of 2 years and <4 years, and 6 months and <2 years.

Indications to be studied:
Maintenance treatment of asthma.

Study design:
Studies 1 and 3: The studies must be randomized, double-blind, placebo-controlled, and crossover. Evaluate four doses of salmeterol and placebo in each of the two studies. In study 1, evaluate a salmeterol dose emitted from the spacers' mouthpieces deemed equivalent to the adult dose of salmeterol on a twice daily schedule, the same dose on a three times daily schedule, and a lower dose on twice and three times daily schedules. The results of study 1 will guide you in selecting the four doses for study 3. In both the studies, treat the patients for at least 7 days.
Study 2 and 4: The studies must be randomized, double blind, double-dummy, placebo-controlled, and parallel group. Evaluate two doses of salmeterol and placebo in each of the two studies. In study 2, evaluate the highest safe dose of salmeterol identified in study 1, and a lower dose. The results of studies 2 and 3 will guide you in selecting the two salmeterol doses for study 4. In both the studies, treat the patients with salmeterol or a matching placebo for at least 4 weeks. Consider the use of rescue inhaled or systemic corticosteroids and other beta$_2$-agonists in the study design.

Age group in which studies will be performed:
Studies 1 and 3: Children between the ages of 2 years and <4 years. Half of the study patients in each treatment group must be below 3 years of age.
Studies 2 and 4: Children between the ages of 6 months and <2 years. Half of the study patients in each treatment group must be below 1 year of age.

Number of patients to be studied:
Studies 1 and 3: A minimum of 20 patients per group (5 groups) per study must complete the studies. Ten patients in each group must use one type of spacer, and the other 10 patients must use a different type of spacer.
Studies 2 and 4: A minimum of 100 patients per group (3 groups) per study must complete the studies. One-half of the study patients must use one type of spacer, and the other half must use a different type of spacer.

Entry criteria:
Children with asthma who are free from other clinically significant medical problems, and expected to derive benefit from salmeterol treatment.

Clinical endpoints:
Studies 1 and 3: The safety endpoints must include heart rate, ECG, blood glucose, serum potassium, and other symptoms and signs of adrenergic stimulation such as, irritability, tremor, lack of sleep, etc. In study 1, attempt to measure peak expiratory flow rate as an efficacy endpoint. Measurement of other efficacy endpoints in study 1, and any efficacy endpoint in study 3 is optional
Studies 2 and 4: The primary efficacy endpoint must include asthma symptom scores such as wheeze, dyspnea, and cough. The secondary efficacy endpoints must include asthma

symptom free days, use of rescue medications, treatment failures, and subject discontinuations. In study 2, attempt to measure peak expiratory flow rate. Safety endpoints must include recording of adverse events, vitals, physical examination, ECG, clinical laboratory measures, and other symptoms and signs of adrenergic stimulation such as, irritability, tremor, lack of sleep, etc.

Study evaluations
Studies 1 and 3: Record heart rate and assess for adrenergic stimulation at least twice daily. Perform ECG, and laboratory measures before treatment and after the 7 days of treatment. In study 1, attempt to record peak expiratory flow rate twice daily.
Studies 2 and 4: Instruct parents or caregivers of the patients to record symptom scores, adverse events, and assess for adrenergic stimulation twice daily on diary cards. Conduct clinic visits every week. During the clinic visits record vital signs, perform physical examination, perform ECG, and assess for adrenergic stimulation. Perform clinical laboratory measures before treatment and at the completion of the treatment. In study 2, attempt to record peak expiratory flow rate twice daily on diary cards.

Drug information:
In all studies use salmeterol xinafoate inhalation aerosol in conjunction with two different U.S.-marketed spacers. The spacers must not replace the actuator of the inhaler. In studies 3 and 4, attach facemasks to the spacer to optimize drug delivery for the very young children. One-half of the patients in the whole program must use one kind of spacer, and the other half must use a different kind of spacer.

Safety concerns:
The safety of salmeterol xinafoate in children between the ages of 6 months and 4 years is unknown. Other than pharmacologically related adverse effects, such as tremors, no unique adverse events are anticipated.

Statistical information:
Studies 1 and 3: Analyze the data by analysis of variance or by an appropriate statistical test for the data.
Studies 2 and 4: Analyze the efficacy data by analysis of variance or by an appropriate statistical test for the data. Perform standard statistical comparisons for adverse events, laboratory values, and other measure.

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 addressing the issues outlined in this request with full analysis, assessment, and interpretation must be submitted to the Agency.

Timeframe:
Full study report must be submitted to the Agency by December 31, 2001.

Before starting the clinical program, characterize the dose delivery from the inhaler with two different spacers with *in vitro* studies to determine the optimum doses for the clinical studies.

We remind you that nonclinical data in juvenile animals of the most appropriate species (e.g., dogs) and of an appropriate developmental stage are required before you administer salmeterol to the very young children. You are encouraged to consult the Division before initiating the nonclinical studies.

Perform the clinical program in sequence, so that the studies on the older children are completed before the younger children. This will help you in dose selection for the younger children from the results of the older children, and give you time to complete the necessary juvenile animal studies.

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. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act)*, with FDA before developing pediatric protocols. 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 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 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 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, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely yours,

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

cc:
Archival NDAs 20-236, (b) (4)
Archival INDs 35,239, (b) (4)
HFD-570/Division File
HFD-570/Hilfiker/PM
HFD-570/Chowdhury/Medical Reviewer/5-14-99
HFD-570/Himmel/Deputy Director/5-14-99
HFD-570/Jenkins/Office Director/5-14-99
HFD-570/Aras/Statistical Reviewer
HFD-570/Wilson/Statistical Team Leader
HFD-570/Schumaker/CPMS/5-14-99
HFD-570/Jani
HFD-570/Meyer
HFD-570/Sancilio
HFD-570/Schroeder
HFD-600/Office of Generic Drugs
HFD-2/Lumpkin
HFD-104/Murphy
HFD-6/Roberts

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5/19/99

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Final by: Hilfiker/5-17-99
Filename: c:\my_documents\Pediatric Exclusivity\salmeterol\99-05-13.wrltr.doc

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)