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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 54,894
NDA 19-957
NDA 20-121
NDA 20-548
NDA 20-549
NDA 20-770
NDA 20-833

5/21/01

GlaxoSmithKline
P.O. 13398
Research Triangle Park, NC 27709

Attention: Betsy J. Waldheim
Product Director
Regulatory Affairs

WRITTEN REQUEST
AMENDMENT #1

Dear Ms. Waldheim:

Reference is made to your correspondence dated February 11, April 14, August 25, October 6, and November 15, 2000, and January 17, 2001, requesting changes to the Pulmonary Section of FDA's June 25, 1999, Written Request for pediatric studies for fluticasone propionate.

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on June 25, 1999, remain the same.

PULMONARY SECTION:

**Objective/rationale:**
Study 1: Assess the efficacy and safety of fluticasone propionate inhalation aerosol delivered with two different spacers in children between the ages of ≥2 years and <4 years, and ≥6 months and < 2 years with asthma.

Study 2: Assess the efficacy and safety of fluticasone propionate inhalation aerosol in children between the ages of ≥2 years and <4 years, and ≥6 months and < 2 years with asthma. All patients may use one type of spacer.

**Number of Patient to be studied:**
Study 1: A minimum of 50 patients per group, of which approximately 1/3 should be less than 12 months of age, must complete the studies. Approximately one-half of the study patients must use one type of spacer, and the other patients must use a different type of spacer

Study 2: A minimum of 50 patients per group, of which approximately 1/3 should be less than 12 months of age, must complete the studies. One type of spacer may be used for all patients in the study.

**Entry criteria:**

Studies 1 and 2: Children with asthma who are free from other clinically significant medical problems, and expected to derive benefit from inhaled corticosteroids. The patients must not have received treatment with greater than 2 courses of systemic or topical corticosteroids within the previous 6 months.

**Study Evaluation**:
Studies 1 and 2: Instruct parents or caregivers of the patients to record symptom scores and adverse events on daily diary cards. In study 1, attempt to record peak expiratory flow rates at least once daily. Conduct clinic visits at least every 4 weeks. During the clinic visits, record vital signs, perform a physical examination including assessment for linear growth, perform oropharyngeal and nasal fungal cultures. Perform clinical laboratory measures and assessments of adrenal function before treatment and at the completion of 12 weeks of treatment. Assess adrenal function by an appropriate test for the study population, such as by measurement of creatinine normalized timed urinary free cortisol excretion, or by an ACTH stimulation test. Assessment of A.M. serum cortisol levels alone will not be adequate. Assess adrenal function in a sufficient number of patients to assure data from at least 24 patients per treatment arm per study who have completed the 12 weeks of treatment. In study 1, approximately half of the 24 patients must use one type of spacer, and the other patients must use a different type of spacer. In study 2, all of the patients may use one type of spacer. (See Drug Information) For study 2, approximately 1/3 of the patients should be less than 12 months of age. For convenience and standardization of the procedure, you may assess adrenal function at a limited number of study centers provided the selected study centers enroll a sufficient number of patients who complete the 12 weeks of treatment. Determine fluticasone plasma levels at the end of 12 weeks of treatment from a subset of an adequate number of patients at appropriate sampling times. If a sufficient amount of data is obtained, a population pharmacokinetic approach may be employed to obtain steady-state fluticasone pharmacokinetic parameters in these patients.

**Drug information:**
Studies 1 and 2: The spacers must not replace the actuator of the inhaler. In study 1, use fluticasone propionate inhalation aerosol in conjunction with two different U.S.-marketed spacers. In study 2, attach appropriate facemasks, available on the U.S. market, to the spacer to optimize drug delivery for the very young children. In study 1, approximately one-half of the patients in each dose group must use one kind of spacer, and the other patients must use a different kind of spacer. In study 2, all patients may use the same type of spacer.

Reports of the studies that meet the terms of the Written Request dated June 25, 1999, as amended by this letter, must be submitted to the Agency on or before July 31, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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. 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 supplements to your approved NDAs, 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 to the pediatric population.

If you have any questions, contact Mrs. Sandy Barnes, Chief, Project Management Staff, at 301-827-1055.

Sincerely,

*{See appended electronic signature page}*

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
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/

John Jenkins
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