HFD-104/Murphy

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

JUN 25 1999

Glaxo Wellcome, Inc.
Attention: Joy E. Ferrell, Director, Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, North Carolina 27709

Dear Ms. Ferrell:

Reference is made to your Proposed Pediatric Study Request submitted on December 15, 1998, for fluticasone propionate.

To obtain needed pediatric information on fluticasone propionate, 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 for both the dermatology and pulmonary indications for fluticasone propionate. The requested studies for the dermatology and pulmonary indications are presented in separate sections of the letter.

PULMONARY SECTION:

Type of studies:
Before starting the clinical program with the inhalation aerosol, characterize the dose delivery from the inhaler with two different U.S.-marketed spacers in *in vitro* studies to determine the optimum doses for Studies 1 and 2 (below).

Study 1: Efficacy and safety of fluticasone propionate inhalation aerosol for maintenance treatment of asthma in children between the ages of ≥2 years and <4 years.
Study 2: Efficacy and safety of fluticasone propionate inhalation aerosol for maintenance treatment of asthma in children between the ages of ≥6 months and <2 years.
Study 3: Safety of fluticasone propionate nasal spray for the treatment of allergic rhinitis in children between the ages of ≥2 years and <4 years.

Perform the clinical program for asthma in sequence, so that Study 1 in older children is completed before initiating Study 2 in younger children. The results from Study 1 will guide you in dose selection for Study 2.

Objective/rationale:
Studies 1 and 2: Assess 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 3: Assess the safety of fluticasone propionate nasal spray on the hypothalamic-pituitary-adrenal (HPA) axis in children between the ages of ≥2 years and <4 years with allergic rhinitis.

Indications to be studied:
Studies 1 and 2: Maintenance treatment of asthma.
Study 3: Allergic rhinitis.

Study design:
Study 1 and 2: The studies must be randomized, double blind, placebo-controlled, and parallel group. Evaluate two doses of fluticasone in each of the two studies. In study 1, evaluate a fluticasone dose emitted from the spacers deemed comparable to a currently approved dose of fluticasone for children above 4 years of age, and a lower dose. The efficacy and safety results of study 1 will guide you in selecting the two fluticasone doses for study 2. In both studies, treat patients with conventional therapy for asthma, and fluticasone or a matching placebo for at least 12 weeks. Consider the use of rescue corticosteroids and beta$_2$-agonists in the study design.
Study 3: The study must be randomized, double-blind, placebo-controlled, and parallel group. Treat the patients with fluticasone or a matching placebo for at least 6 weeks.

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

Number of patients to be studied:
Studies 1 and 2: 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.
Study 3: A minimum of 24 patients per study group (2 groups) must complete 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 study patients must not have used any systemic or topical corticosteroids within 6 months of the study.
Study 3: Children with allergic rhinitis who may derive benefit from intranasal corticosteroids. The study patients must not have used any systemic or topical corticosteroids within 6 months of the study and must be free from other clinically significant medical problems.

Clinical endpoints:
Studies 1 and 2: 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 patients discontinuations. In study 1, attempt to measure peak expiratory flow rate. Safety endpoints must include recording of adverse events, vital signs, physical examination, linear growth, HPA-axis assessment, and clinical laboratory measures.
Study 3: Assess the effect of fluticasone propionate nasal spray on the hypothalamic-pituitary-adrenal (HPA) axis. A global efficacy assessment based on parent or caregiver ratings of patient symptoms at the start of the study period and at the completion of 6 weeks of treatment is optional.

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, and 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, and measure fluticasone plasma levels 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 AM 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. Half of the 24 patients must use one type of spacer, and the other half must use a different type of spacer (see **Drug Information**). For study 2, at least 8 of these patients per group must be below 1 year old. 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.
Study 3: Instruct parents or caregivers to record adverse events on daily diary cards. Perform a physical examination, clinical laboratory measures, an assessment of adrenal function before treatment and at the completion of 6 weeks of treatment, and an assessment of fluticasone plasma levels at the completion of 6 weeks of treatment. Assess adrenal function by an appropriate test, such as by measurement of creatinine normalized timed urinary free cortisol excretion, or ACTH stimulation test. Assessment of AM serum cortisol levels alone will not be adequate. Determine fluticasone plasma levels at the end of 6 weeks of treatment from these 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:
Use fluticasone propionate inhalation aerosol in conjunction with two different U.S.-marketed spacers. The spacers must not replace the actuator of the inhaler. In study 2, attach appropriate facemasks, available on the U.S. market, to the spacers to optimize drug delivery for the very young children. One-half of the patients in each dose group must use one kind of spacer, and the other half must use a different kind of spacer.
Study 3:
Use fluticasone propionate nasal spray (50 mcg/actuation) at a dose of 200 mcg/day.

Drug specific safety concerns:
The safety concerns with nasal and orally inhaled corticosteroids are suppression of adrenal function, suppression of linear growth, and adverse effects and other effects associated with corticosteroids. Oropharyngeal fungal overgrowth is also of concern with orally inhaled corticosteroids.

Statistical information, including power of study and statistical assessments:
Study 1 and 2: 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 measures.
Study 3: Adrenal function data must be analyzed using Student's t-test with baseline as a covariate. Standard descriptive statistical analyses must be performed for adverse events, laboratory values, and other safety measures.

DERMATOLOGY SECTION:
Type of studies:
Studies 1 and 2: Safety and efficacy of fluticasone propionate lotion, 0.05%, for treatment of moderate to severe atopic dermatitis in children between the ages of 3 months to 5 years.
Study 3: Safety of fluticasone propionate lotion, 0.05%, for the treatment of moderate to severe atopic dermatitis. An open label adrenal suppression study of fluticasone propionate lotion, 0.05%, used twice daily in pediatric subjects aged 3 months to 5 years with moderate to severe atopic dermatitis.
Study 4: Safety of fluticasone propionate ointment, 0.005%, for the treatment of corticosteroid responsive dermatoses. An open label adrenal suppression study of fluticasone propionate ointment, 0.005%, used twice daily in pediatric subjects aged 3 months to 5 years with moderate to severe atopic dermatitis.

Objective/rationale:
Studies 1 and 2: Assess the safety and efficacy of fluticasone propionate lotion, 0.05%, applied once daily for up to four weeks to that of the vehicle lotion in children between the ages of 3 months to 5 years with moderate to severe atopic dermatitis.
Study 3: Assess the safety of fluticasone propionate lotion, 0.05%, on the hypothalamic-pituitary-adrenal (HPA) axis in children between the ages of 3 months and 5 years with moderate to severe atopic

dermatitis, and also assess local cutaneous effects and other systemic effects of fluticasone propionate lotion,0.05%.
Study 4: Assess the safety of fluticasone propionate ointment, 0.005%, on the hypothalamic-pituitary-adrenal (HPA) axis in children between the ages of 3 months and 5 years with moderate to severe atopic dermatitis and also assess local cutaneous effects and other systemic effects of fluticasone propionate ointment, 0.005%.

Indication to be studied:
Studies 1 and 2: Moderate to severe atopic dermatitis, a subset of the indication, "corticosteroid-responsive dermatoses."
Study 3: Moderate to severe atopic dermatitis, a subset of the indication, "corticosteroid-responsive dermatoses."
Study 4: Moderate to severe atopic dermatitis, a subset of the indication, "corticosteroid-responsive dermatoses."

Study design:
Studies 1 and 2: Both studies should be randomized, double-blind, parallel group, vehicle controlled. Assess the safety and efficacy of fluticasone propionate compared to the vehicle when used for up to 4 weeks. The primary investigator may, at his or her discretion, discontinue any subject from participating in these studies if safety concerns develop.
Studies 3 and 4: The studies should be open-label, multi-centered.

Age group in which studies will be performed:
Studies 1 and 2: Children enrolled in the studies should be between the ages of 3 months and 5 years.
Studies 3 and 4: Children enrolled in the studies should be between the ages of 3 months and 5 years, with 10-15 patients in the age group 3 months – 2 years old and 10-15 patients in the age group 3 years-5 years old.

Number of patients to be studied:
Studies 1 and 2: 100 pediatric patients (50 in each treatment group) for each study.
Study 3: A minimum of 30 evaluable patients must complete the study.
Study 4: A minimum of 30 evaluable patients must complete the study.

Entry criteria:
Studies 1 and 2: Moderate to severe atopic dermatitis as determined by an ordinal severity scoring scale.
Studies 3 and 4: Moderate to severe atopic dermatitis as determined by an ordinal severity scoring scale. Subjects with greater than or equal to 35% of body surface area involved, not including the diaper area.

Clinical endpoints:
Studies 1 and 2: The primary efficacy variable should be based on a clinical signs/symptoms scoring scale that is dichotomized to success/failure.

Study 3: Demonstration of HPA axis function which should be determined by response to cosyntropin testing, in which age appropriate doses of cosyntropin are administered. Data should be provided from a single, validated assay. Clinical assessments should include medical history/baseline disease and medications, physical examination, dermatologic evaluations (such as signs of skin atrophy, skin pigmentation changes, telangiectasia), assessment of compliance with treatment, and routine clinical laboratory tests.
Study 4: Demonstration of HPA axis function which should be determined by response to cosyntropin testing, in which age appropriate doses of cosyntropin are administered. Data should be provided from a single, validated assay. Other systemic safety parameters should be obtained through routine clinical laboratory tests. Clinical assessments should include medical history/baseline disease and medications, physical examination, dermatologic evaluations (i.e., investigators' directed evaluation of changes from baseline at any visit in the local intolerance profile known to be associated with topically applied glucocorticoids, viz., telangiectasia, thinness, shininess, striae, bruising, loss of elasticity and loss of normal skin markings).

Drug information:
Studies 1 and 2: Use fluticasone propionate lotion, 0.05%, once daily for up to four weeks.
Study 3: Use fluticasone propionate lotion, 0.05%, twice daily for 3-4 weeks.
Study 4: Use fluticasone propionate ointment, 0.005%, twice daily for 3-4 weeks.

Safety concerns:
The safety concerns are suppression of adrenal function and other systemic effects associated with corticosteroids, such as glucose metabolism, fluid/electrolyte balance, hematologic parameters, and local cutaneous effects.

Statistical information:
Studies 1 and 2: Analyze the efficacy data by an appropriate statistical test for the data. Perform standard descriptive statistics for adverse events, laboratory values, and other measures.
Studies 3 and 4: Standard descriptive statistical analyses must be performed for adverse events, laboratory values, and other safety measures. Study 4 should provide a subgroup analysis for use of fluticasone propionate ointment, 0.005%, on the face.

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 for submitting reports of the studies:
Full study reports for all requested studies must be submitted to the Agency by December 31, 2001.

You are strongly encouraged to develop an inhalation solution or suspension formulation for nebulization that is more appropriate for treating asthma in the pediatric population requested in the

above studies. However, the development and approval of such a formulation is not required in order for pediatric exclusivity to be awarded as a result of this letter.

Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your reports of the 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. 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 supplements to your approved NDAs and/or new drug applications 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, contact David Hilfiker, Project Manager, at 301-827-1050, or Millie Wright, Project Manager, at 301 827-2020.

Sincerely yours,

RJD. 6/23/1999

Robert J. DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

cc:
NDA 19-957
NDA 19-084
NDA 20-121
NDA 20-548
NDA 20-549
NDA 20-770
NDA 20-833
IND 54,894
IND (b) (4)
IND (b) (4)
IND (b) (4)
IND 53,502
IND 57,151
HFD-570/division file
HFD-570/Chowdhury/Uppoor/Chen/ 6/18/99
HFD-570/Himmel
HFD 570/Hilfiker/6/18/99
HFD-570/Schumaker/6/16/99
HFD-540/division file
HFD-540/Kozma-Fornaro/6/22/99
HFD-540/Cook/6/16/99
HFD-540/Walker/6/16/99
HFd-540/Wright
HFD 880/Bashaw
[redacted]
HFD-600/Office of Generic Drugs
HFD-2/Lumpkin
HFD-2Crescinzi
HFD-104/Hassall

Concurrence Only:
HFD-570/ActDivDir/Meyer
HFD-540/DivDir/Wilkin/6/16/99

Drafted by: MJKF5/28/99
MW/6/12/99;6/14/99;6/18/99
Initialed by:
Final: 6/22/99

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)