HFD-570 WR

NDA 20-625
NDA 20-786
NDA 20-872

4/23/01

Aventis Pharmaceuticals
Somerset Corporate Center
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807-2584

Attention: J. Michael Nicholas, Ph.D.
Vice President
US Drug Regulatory Affairs & Compliance

WRITTEN REQUEST #2

Dear Mr. Vallee:

Reference is made to your Proposed Pediatric Study Request to IND 51,709, submitted on December 8, 2000, for fexofenadine hydrochloride.

To obtain needed pediatric information on fexofenadine, the Food and Drug Administration (the Agency) 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:

Types of Studies to be Performed

Study 1: Pharmacokinetic and safety study in pediatric patients ≥6 months to <2 years of age

Study 2: Safety study in pediatric patients >6 months to <2 years of age

Perform Study 1 first to determine the appropriate dose(s) to be used in Study 2.

Objective/Rationale

Study 1: To assess the pharmacokinetics of fexofenadine in order to determine the dose for patients ≥6 months to <2 years of age that results in comparable concentrations and exposures (i.e., C_{max} and AUC) of fexofenadine to those seen in adolescents and adults given labeled doses of fexofenadine. You should use these data to determine the appropriate dosage by age and/or by weight for safety assessment in Study 2.

Study 2: To assess the safety of fexofenadine in patients ≥6 months to <2 years of age when administered at an age- and/or weight-appropriate dose.

Indications to be Studied: Allergic rhinitis, or urticaria, or other conditions that are appropriately treated with antihistamines.

Study Design

Study 1: Perform a single- or multiple-dose pharmacokinetic study with one or more dose levels of fexofenadine to evaluate an age- and/or weight-appropriate dose. Either a conventional or population pharmacokinetic study is acceptable; however, for each patient, obtain a minimal amount and limited number of blood samples at adequate sampling times to evaluate pharmacokinetics appropriately. Sampling times may be selected based on an optimum sampling strategy for the best estimation of the pharmacokinetics of fexofenadine.

Study 2: Perform a randomized, double-blind, placebo-controlled, parallel-group safety study with a treatment duration of at least one week of a single age- and/or weight-appropriate dose utilizing an age-appropriate dosage form of fexofenadine. Select the dose based on results of Study 1.

Age Group in Which Studies Will Be Performed

Studies 1 and 2: Children ≥6 months to <2 years of age distributed in a ratio of approximately 1:2 between the following age groups: ≥6 months to <1 year and ≥1 to <2 years. Appropriate representation of children of various ages across the age range of ≥6 months to <1 year should be achieved.

Number of Patients to be Studied

Study 1: For a conventional pharmacokinetic study, a minimum of 18 children per dose level must complete the study, with at least 6 patients in each of the two following age groups: ≥6 months to <1 year and >1 to <2 years. For a population pharmacokinetic study, a minimum of 50 children per dose level must complete the study, with at least 15 patients for each dose level studied in each of the two following age groups: ≥6 months to <1 year and ≥1 to <2 years.

Study 2: A total of at least 100 children per treatment arm (i.e., a total of at least 200 patients for the study) must complete the study. As an alternative, a total of at least 50 children per treatment arm (i.e., a total of at least 100 patients for the study) must complete the study for a study duration of two weeks.

Entry Criteria

Studies 1 and 2: Children ≥6 months to <2 years of age who are either current candidates for antihistamine therapy or who have tolerated a therapeutic course of antihistamine in the past.

Clinical Endpoints

Study 1: Determine the plasma concentration of fexofenadine using the same validated assay method employed previously or using an adequately cross-validated assay method. Safety endpoints must include adverse events, vital signs, physical examinations, and ECGs. Adverse events must be recorded in a diary record. Vital signs and physical examinations must be performed at screening or baseline and at the end of the study. If a single-dose study is performed, a twelve-lead ECG should be performed at the estimated T_{max}. If a multiple-dose study is performed, clinical chemistries, and hematology profiles must be performed at screening or baseline, and at steady-state, and ECGs should be performed at baseline or screening, at the time of estimated T_{max} after the initial dose, and at the time of estimated T_{max} after steady-state is achieved.

Study 2: Safety endpoints must include adverse events, vital signs, physical examinations, and appropriately timed ECGs. Adverse events must be recorded in a diary record. Vital signs, physical examinations, and 12-lead ECGs must be performed at screening or baseline and toward the end of the study while participants are still on study drug.

Study Evaluations

Study 1: Report plasma concentrations and estimated apparent oral clearance of fexofenadine. Report pharmacokinetic parameters such as C_{max}, T_{max}, AUC, and $T_{1/2}$ for fexofenadine. Effects of covariates, such as age, weight, height, and body surface area, should be studied. For study of

these effects of covariates, utilize appropriate prior pharmacokinetic data available in children and adults. Reported safety data must include descriptive analyses of changes in vital signs, physical examinations, ECGs, and adverse reactions. Clinical chemistries and hematology profiles should be included if a multiple-dose study is performed.

Study 2: Safety data must include changes in vital signs, physical examinations, ECGs, and adverse reactions.

Drug Information

Studies 1 and 2:

Dosage form: Age-appropriate dosage form (for which relative bioavailability has been established)

Route of administration: Oral

Regimen:

Study 1: Single- or multiple-dose administration of one or more dose levels at age- and/or weight-appropriate doses

Study 2: Repeat-dose administration on multiple days of an age- and/or weight-appropriate dose with dosing intervals as determined by pharmacokinetic and other related data

Safety Concerns

Unanticipated adverse reactions, particularly paradoxical excitability, somnolence, fatigue, and/or hyperkinesia.

Statistical Information

Study 1: Provide pharmacokinetic parameters and descriptive analyses of vital signs, physical examinations, ECGs and adverse events. Include descriptive analyses of laboratory studies if a multiple-dose study is performed.

Study 2: Provide descriptive analyses of adverse events, vital signs, physical examinations, and ECGs.

Labeling That May Result from the Studies

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

Format of Reports to be Submitted

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for Submitting Reports of the Studies

Reports of the above studies must be submitted to the Agency on or before January 31, 2003. Please keep in mind that pediatric exclusivity only attaches to 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. 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 New Drug Application or 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 amendment 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 in this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Ms. Gretchen Trout, Regulatory Project Manager, at (301) 827-1058.

Sincerely yours,

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