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NDA 20-929

DEC 14 1998

Astra Pharmaceuticals, L.P.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Attention: Michael Elia, Ph.D.
Director
Regulatory Liaison

Dear Dr. Elia:

Reference is made to your ~~Proposed~~ Pediatric Study Request submitted on March 5, 1998 for Pulmicort Respules (budesonide inhalation suspension) to NDA 20-929.

To obtain needed pediatric information on budesonide, 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: Efficacy and safety of budesonide nebulizing suspension for treatment of asthma in children between the ages of 6 months and 1 year.

Study 2: Safety of budesonide nasal spray in children between the ages of 2 years and 6 years.

Rationale:

Study 1: The efficacy and safety of budesonide nebulizing suspension in children below the age of 1 year is not known.

Study 2: The effect of budesonide nasal suspension on the hypothalamic-pituitary-adrenal (HPA) axis in children between the ages of 2 years and 6 years is not known.

OK per Dr Hammerl

Indications to be studied:

Study 1: Asthma.

Study 2: Allergic rhinitis.

Study design:

Study 1: The study must be randomized, double blind, placebo-controlled, and parallel group. The study subjects are to be randomized into 3 groups: a control group, and 2 treatment groups of 0.5 mg/day and 1 mg/day of budesonide. The control group should be given conventional therapy for asthma, but not inhaled corticosteroids. The treatment groups should be given conventional therapy for asthma, and inhaled budesonide. The study subjects must be treated with budesonide or matching vehicle placebo for 12 weeks. The study design must take into consideration use of rescue inhaled or systemic corticosteroids.

Study 2: The study must be randomized, double blind, placebo-controlled, and parallel group. The study subjects are to be randomized into 2 groups: a control group, and a treatment group of 64 mcg/day of budesonide. The study subjects must be treated with budesonide or matching vehicle placebo for 6 weeks.

Age Group in Which Studies will be Performed:

Study 1: Children between the ages of 6 months and 1 year. Approximately half of the study subjects in each study group must be below 9 months of age. In addition, there must be at least 15 subjects each for the age groups of ≥6 months and <7 months, ≥7 months and <8 months, and ≥8 months and <9 months in each of the 3 study groups.

Study 2: Children between the ages of 2 years and 6 years. There must be at least 6 subjects each for the age groups of ≥2 years and <3 years, ≥3 years and <4 years, ≥4 years and <5 years, ≥5 years and <6 years in each of the 2 study groups.

Number of Subjects to be studied:

Study 1: A minimum of 135 subjects per study group (3 groups) must complete the study.

Study 2: A minimum of 24 subjects per study group (2 groups) must complete the study.

Entry criteria:

Study 1: Children between the ages of 6 months and 1 year with moderate asthma who may derive benefit from inhaled corticosteroids. The study subjects should

not have been exposed to inhaled or systemic corticosteroids and should be free from other clinically significant medical problems.

Study 2: Children between the ages of 2 and 6 years with rhinitis who may derive benefit from intranasal corticosteroids. The study subjects 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:

Study 1: The primary efficacy measure must comprise asthma symptom scores, and the secondary efficacy measures must include, use of rescue medications, treatment failures, and subject discontinuations.

Study 2: No efficacy measure is required. 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:

Study 1: The efficacy evaluations must include parent or caregiver ratings of patient asthma symptom scores, use of rescue medications, treatment failures, and subject discontinuations. These must be assessed at least every 4 weeks. Safety measures must include recording of adverse events, physical examination, oropharyngeal and nasal fungal cultures, and assessment of linear growth. These must be performed before treatment and at least every 4 weeks. Serum chemistry and hematology, and assessment of adrenal function must be performed before treatment, and at the completion of 12 weeks of treatment. Adrenal function must be assessed by an appropriate test for the study population, such as by an ACTH stimulation test of HPA-axis, or by measurement of (b) (4) A single measurement of AM cortisol level will not be adequate. The assessment of adrenal function must be performed in at least 24 subjects in each study group who complete 12 weeks of the study treatment (at least 8 patients per group must be <8 months old). For convenience and standardization of the procedure, the assessment of adrenal function may be performed at a limited number of study centers provided the selected study centers enroll a sufficient number of study subjects who complete the 12 weeks of treatment to achieve the required minimum number of subjects assessed.

Study 2: The study evaluations must include recording of adverse events, physical examination, serum chemistry and hematology, and assessment of adrenal function performed before treatment, and at the completion of 6 weeks of

treatment. Adrenal function must be assessed by an appropriate test for the study population, such as by an ACTH stimulation test of HPA-axis, or by measurement of [redacted] (b) (4) A single measurement of AM cortisol level will not be adequate.

Drug information:

Study 1: Dosage form: Pulmicort 2 mL Respules.
Route of administration: Delivery into the lung by jet nebulizer.
Regimen: One or two nebulized treatments/day (total dose: 0.5 mg/day and 1 mg/day).

Study 2: Dosage form: Rhinocort Aqua Nasal Spray 32 mcg.
Route of administration: Topical intranasal.
Regimen: One spray to each nostril/day (64 mcg/day).

Safety concerns:

Study 1: The safety concerns are reduction of linear growth, suppression of adrenal function, oropharyngeal fungal overgrowth, topical airway adverse reaction, and other effects associated with corticosteroids.

Study 2: The safety concerns are suppression of adrenal function, and other effects associated with corticosteroids.

Statistical information:

Study 1: The sample size of 135 patients per group is calculated to detect a mean difference of 0.25 in the asthma symptoms score (0-3 scale) recorded every 12 hours, averaged for the 12 weeks of treatment, with a power of 80% at an alpha level of 0.05. The standard deviation used in the calculation was 0.73. Analysis of variance with appropriate covariates (e.g. baseline symptom scores) must be performed. The covariates must be prespecified in the protocol. The primary efficacy analysis must be a step-down procedure that first compares the higher dose to placebo at 0.05 level and if significant, compares the lower dose to placebo at the same level. This will guarantee that the overall type one error remains at most 0.05. All the pairwise comparisons must be reported. Linear growth must also be analyzed similarly.

Study 2: Adrenal function data must be analyzed using Student's t-test with baseline as a covariate. Standard statistical comparisons must be performed for adverse events, laboratory values, and other measures.

Labeling that may result from the studies:

Study 1: The indicated age may be reduced down to 6 months.

Study 2: The appropriate sections may be updated to incorporate the information.

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 reports must be submitted to the Agency by December 31, 2000.

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. J. Lindsay Cobbs, Project Manager, at (301) 827-1051.

Sincerely yours,

Florence Haam MD for

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-929
HFD-570/division file
HFD-570/Cobbs
HFD-570/Chowdhury
HFD-570/Honig
HFD-570/Himmel
HFD-570/Jenkins
HFD-570/Aras
HFD-570/Wilson
HFD-102/Bilstad
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6/KRoberts
Drafted by: Chowdhury/Cobbs
Initialed by: SCHUMAKER/12-11-98
HIMMEL/12-14-98
Final: CAMPBELL/12-14-98
filename: N:/MY DCOUMENTS/N20929WR.DOC
PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

12-14-98

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