DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-929

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

Attention: Christopher Blango
Director, Regulatory Affairs

WRITTEN REQUEST
Amendment #4

Dear Mr. Blango:

Please refer to your correspondence dated December 7, 2001, requesting changes to FDA's December 14, 1998, December 22, 1999, May 22, 2000, and June 6, 2001, Written Requests for pediatric studies for budesonide.

We reviewed your proposed changes and are amending the below listed sections of the Written Request, specifically Study 1. All terms relating to Study 2 stated in our Written Request issued on December 14, 1998, remain the same.

Type of study:

Study 1: Safety of budesonide nebulizing suspension for treatment of asthma in children between the ages of 6 months and 1 year, with efficacy parameters assessed as secondary endpoints.

Rationale:

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

Indication to be studied:

Study 1: Asthma.

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 no inhaled corticosteroids. The treatment groups should be given conventional therapy for asthma, and inhaled budesonide. The duration of study treatment with budesonide or matching vehicle placebo should be 12 weeks.

The study design must take into consideration use of rescue inhaled or systemic corticosteroids.

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.

Number of subjects to be studied:

Study 1: At least 90 children must complete the study, approximately two-thirds of whom must have received active treatment.

Entry criteria:

Study 1: Children between the ages of 6 months and 1 year with asthma or asthma-like signs and symptoms who are likely to benefit from inhaled corticosteroids. The subjects should not have received systemic corticosteroids for at least 4 weeks and should have no known or suspected endocrine abnormality (based on medical history). Subjects who have received inhaled corticosteroids may be recruited; however, they must undergo a minimum of a 2-week "washout" prior to entry into the trial.

Clinical endpoints:

Study 1: Efficacy will be considered a secondary assessment for purposes of this study. At least three efficacy parameters should be assessed and may include asthma symptom scores, use of rescue medications, asthma episodes, and subject discontinuations due to treatment failures. Efficacy evaluations must be made at the start of the study and reassessed every 4 weeks thereafter.

Study evaluation:

Study 1: The efficacy evaluations may include parent or caregiver ratings of patient asthma symptom scores, use of rescue medications, asthma episodes, and subject discontinuations due to treatment failures. These should be assessed at least every 4 weeks. Safety measures should include recording of adverse events, physical examination, oropharyngeal and nasal fungal cultures, and assessment of linear growth. These should be performed before treatment and at least every 4 weeks. Serum chemistry and hematology should be performed before treatment, and at the end of the study. Assessment of adrenal function must be performed before treatment, and at the

completion of the study. 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 timed urinary free cortisol excretion. A single measurement of AM cortisol level will not be adequate. The assessment of adrenal function must be performed in at least 72 subjects who complete the study, at least two-thirds of whom must have received active treatment (at least 12 patients per active treatment group must be <9 months old at enrollment). 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 study to achieve the required minimum number of subjects assessed.

Drug information:

Study 1: Dosage form: Pulmicort Respules 2 mL.

Route of administration: Delivery into the lung by jet nebulizer.

Regimen: One or two nebulized treatments/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

Statistical information:

Study 1: The safety data should be tabulated and standard summary statistics should be utilized. Efficacy parameters should be evaluated using appropriate analyses, including summary statistics and inferential testing. Because of power considerations, a demonstration of statistically significant differences is not expected.

Labeling that may result from the studies:

Study 1: The appropriate sections of the product label may be updated to incorporate the information.

Timeframe:

Study 1: The full study reports must be submitted to the Agency by September 3, 2002.

Reports of these studies that meet the terms of the Written Request dated December 14, 1998, as amended by this letter must be submitted to the Agency on or before September 3, 2002, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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. 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.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, 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, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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, call Colette Jackson, Project Manager, at 301-827-5580.

Sincerely,

{See appended electronic signature page}

Robert Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

HFD-570/division file
HFD-570/Jackson
HFD-570/Barnes
HFD-570/Purucker
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HFD-600/Office of Generic Drugs

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PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer

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