DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-344

AstraZeneca Pharmaceuticals, LP
Attention: Katherine Gans-Brangs, PhD
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Gans-Brangs:

Reference is made to your Proposed Pediatric Study Request submitted to IND 62,195 on July 1, 2002, for Faslodex (fulvestrant) Injection.

To obtain needed pediatric information on fulvestrant, 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:

TYPES OF STUDIES

Study 1. A population pharmacokinetic (PK) study of fulvestrant in girls with McCune-Albright Syndrome (MAS) and progressive precocious puberty (PPP).

Study 2. A one-year, open-label, multicenter study to assess the efficacy and safety of fulvestrant in the treatment of PPP in girls with MAS.

INDICATION TO BE STUDIED

Treatment of PPP in girls with MAS.

OBJECTIVE/RATIONALE

Study 1. To assess the pharmacokinetics of fulvestrant in girls with precocious puberty associated with MAS.

Study 2. To assess the safety and effectiveness of fulvestrant in slowing the progression of puberty in girls with precocious puberty associated with MAS.

AGE GROUP IN WHICH STUDIES WILL BE PERFORMED

Study 1. Girls ≤ 10 years of age. Approximately 50% of patients should be < 7 years of age.

Study 2. Girls ≤ 10 years of age. Approximately 50% of patients should be < 7 years of age.

NUMBER OF PATIENTS TO BE STUDIED

Study 1. At least twenty patients with complete PK data.
Study 2. At least twenty patients treated for one year with sufficient efficacy and safety data.

STUDY ENDPOINTS

Study 1.

1. Mean clearance and volume of distribution of fulvestrant.
2. Body weight and race effect on fulvestrant PK should also be explored.

Study 2.

1. Change in frequency and duration of annualized episodes of vaginal bleeding on treatment compared to baseline.
2. Proportion of patients with baseline vaginal bleeding who experienced ≥50% reduction in the number of vaginal bleeding episodes on treatment.
3. Proportion of patients with baseline vaginal bleeding who experienced cessation of menses over a 6-month trial period and over the whole 12-month trial.
4. Change in bone age advancement on treatment compared to change during baseline (provide data for both the 6-month and the 12-month timepoints).
5. Change in growth velocity on treatment compared to change during baseline (provide data for both the 6-month and the 12-month timepoints).

ADDITIONAL ASSESSMENTS

1. Change in Tanner stage (breast and pubic hair) at the 12-month timepoint relative to baseline.
2. Change in uterine volume at the 6-month and 12-month timepoints relative to baseline uterine volume.
3. Change in ovarian volume at the 6-month and 12-month timepoints relative to baseline ovarian volume (categorization of the number and size of ovarian cysts should be attempted).
4. Predicted adult height at the 12-month timepoint trial relative to baseline.
5. Tolerability and safety data.

STUDY DESIGN

Study 1. The open-label population PK study can be conducted in patients who will be enrolled in Study 2. Patients will receive monthly intramuscular injections of 2 mg fulvestrant/kg body weight. Four blood samples will be collected from each patient after the initial dose such that one blood sample will be randomly collected per week. Fixed sampling times should be avoided. Timing of blood samples should be such that the entire time course of plasma fulvestrant concentrations can be accurately captured after the initial dose. Times of monthly dose administration and blood sample collection should be recorded. Patients will receive another intramuscular 2 mg/kg injection for the second month. If presumed plasma fulvestrant therapeutic concentrations cannot be achieved from the 2 mg/kg dose, patients will receive

monthly intramuscular injections of 4 mg fulvestrant/kg body weight thereafter. One more blood sample will be collected from each patient after approximately seven months of treatment to confirm the trough steady-state plasma fulvestrant concentration.

Study 2. An open-label, noncomparative, multicenter, one-year, safety and efficacy study of fulvestrant in girls with MAS. The study will include a 6-month, prospective, pre-study (baseline) period. This prospective observational period may be one during which previous therapy occurred.

STUDY ENTRY CRITERIA

Studies 1 and 2. Girls with classical or atypical MAS associated with PPP manifested by signs of pubertal development, menses, and/or advanced bone age (advanced bone age of at least 12-months greater than chronological age). The criteria applied for the diagnosis of MAS and PPP in each patient should be clearly stated. Approximately equal numbers of treatment naïve patients and non-naïve patients who failed other therapies should be enrolled. A 6-month prospective observational period prior to study treatment will be included for collection of bone age, height, and vaginal bleeding data. All bone age X-ray readings should be centralized and performed by experienced reader(s) in a blinded fashsion.

DRUG INFORMATION

- Dosage form: solution for injection
- Route of Administration: intramuscular
- Regimen: Study 1: 2 mg/kg of fulvestrant per body weight monthly (4 mg/kg pending PK prediction)

  Study 2: to be determined by the PK study
- Formulation: marketed

DRUG-SPECIFIC SAFETY CONCERNS

Injection site reactions, gastrointestinal symptoms, headache, urinary tract infections, pharyngitis.

STATISTICAL INFORMATION, INCLUDING POWER OF STUDY AND STATISTICAL ASSESSMENTS

Study 1. Descriptive statistics for the above mentioned PK endpoints.

Study 2. Paired t tests will be used to compare mean growth rate, mean bone age advancement, and mean frequency and duration of vaginal bleeding episodes during baseline period to the mean rates during treatment. A ninety-five percent confidence interval should also be constructed for the mean differences between treatment and baseline. Appropriate nonparametric methods will be used if assumptions for the t tests are not satisfied. Correlations between growth velocity changes and bone age changes should be performed.

Descriptive statistics should be presented for all study endpoints. Descriptive statistics for continuous endpoints should include sample size, mean, standard deviation, median, and range, as well as individual changes.

You should conduct two sets of analyses: (1) all patients exposed to treatment and (2) a protocol valid analysis.

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 not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies must be submitted to the Agency on or before January 26, 2007. 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 studies in response to this Written Request.

RESPONSE TO WRITTEN REQUEST

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

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 (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 Monika Johnson, PharmD, Regulatory Project Manager, at 301-827-6370.

Sincerely,

Robert J. Meyer, MD
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Robert Meyer

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