DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-344
IND 62,195

WRITTEN REQUEST
AMENDMENT # 2

AstraZeneca Pharmaceuticals, LP
Attention: Kathleen Gans-Brangs, Ph.D.
Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Gans-Brangs:

Please refer to your correspondence submitted to IND 62,195 dated November 30, 2004, requesting changes to FDA's October 21, 2002, Written Request as amended May 7, 2004, for pediatric studies for Faslodex (fulvestrant) injection.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the amended Written Request follows with changes shown in **bold** text. This Written Request supersedes the Written Request dated October 21, 2002, as amended May 7, 2004.

We also refer to the Agency's March 3, 2005, minutes of our February 1, 2005, teleconference with your firm and your firm's March 15, 2005, request to correct those minutes. Our response to your request appears at the end of this letter.

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. **It is recommended that** approximately 50% of patients should be < 7 years of age.

Study 2. Girls ≤ 10 years of age. **It is recommended that** approximately 50% of patients should be < 7 years of age.

NUMBER OF PATIENTS TO BE STUDIED

Study 1. At least twenty patients with **sufficient** 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 of annualized episodes of vaginal bleeding on treatment compared to baseline (collection of data on the duration of vaginal bleeding is, whenever possible, strongly recommended).**
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 may be a substudy of 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. **Both treatment naïve and non-naïve patients who failed other therapies may be enrolled. A minimum of six months retrospective and/or prospective data will be obtained for bone age, height, and vaginal bleeding.** All bone age X-ray readings should be centralized and performed by experienced reader(s) in a blinded fashion.

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:* **Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be**

compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

[Please note that the added requirement to develop an age- appropriate formulation is now standard in all Written Requests. However, we believe that your marketed injectable product will likely fulfill this requirement.]

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, mean frequency of annualized episodes of vaginal bleeding, and whenever possible, mean 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. All pediatric patients enrolled in the studies **should** be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, one of the following designations **should** be used: Hispanic/Latino or Not Hispanic/Latino.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

- Reports of the above studies must be submitted to the Agency on or before **March 31, 2011**. Please keep in mind that pediatric exclusivity attaches only 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. 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.

Submit reports of the studies as a **new drug application (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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov and http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

We agree with the points raised in your March 15, 2005, correspondence in which you requested correction of the Agency's March 3, 2005, minutes. Those points have been corrected in this written request, but revised minutes will not be issued.

Our responses to each of your comments follows:

> Comment #1. We agree that one amendment to the fulvestrant WR was issued previously, on May 7, 2004, and therefore, this is the second amendment to the WR.

Comments # 2 & 3. The Agency's minutes incorrectly used the phrase "Girls = 10 years of age" instead of "Girls ≤ 10 years of age" when discussing the ***AGE GROUP IN WHICH STUDIES WILL BE PERFORMED***.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, Division of Metabolic and Endocrine Drug Products, at 301-827-6429.

Sincerely,

{See appended electronic signature page}

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

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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