DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-498
PIND 61,238

AstraZenenca Pharmaceuticals, Inc.
Attention: Lisa V. DeLuca, PhD
Director, Regulatory Affairs
1800 Concord Pike
Wilmington, DE 19803-8355

WRITTEN REQUEST

Dear Dr. DeLuca:

Reference is made to your Proposed Pediatric Study Request submitted on December 13, 2002, to Pre-IND 61,238 for Casodex (bicalutamide) tablets.

To obtain needed pediatric information on bicalutamide, 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. A relative bioavailability (BA) study between a pediatric bicalutamide oral liquid formulation (to be developed) and the marketed 50 mg bicalutamide oral tablet.

Study 2. A relative BA study between a pediatric anastrozole oral liquid formulation (to be developed) and the marketed 1 mg anastrozole oral tablet.

Study 3. An efficacy study of bicalutamide and anastrazole.

Objectives/Rationale:

Study 1. To investigate the relative BA of bicalutamide between a pediatric liquid formulation and the marketed tablet in adults.

Study 2. To investigate the relative BA of anastrozole between a pediatric liquid formulation and the marketed tablet in adults.

Study 3. To assess the efficacy and safety of bicalutamide when used in combination with anastrazole for the treatment of precocious puberty in boys with testotoxicosis.

Indication to be studied:

Treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis.

Study design:

Study 1. This is a randomized, open-label, crossover study in healthy adult volunteers, who will receive orally 50-mg bicalutamide in either liquid or tablet form in the first treatment period. After a washout period of at least 63 days, the subjects will receive 50-mg bicalutamide in either liquid or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma bicalutamide concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 2. This is a randomized, open-label, crossover study in healthy adult volunteers, who will receive orally 1-mg anastrozole in either liquid or tablet form in the first treatment period. After a washout period of at least 20 days, the subjects will receive 1-mg anastrozole in either liquid or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma anastrozole concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 3. A twelve-month, open-label, multicenter, observational study of bicalutamide used in combination with anastrazole in boys with testotoxicosis. The study will have at least 12 evaluable patients with complete efficacy and safety data at the end of one year of treatment. All patients must be naïve to antiandrogen therapy. The occurrence of central precocious puberty (CPP) will be monitored and will include a GnRH stimulation test at regular intervals or at any point where the investigator believes CPP has occurred. If CPP develops, treatment with a GnRH agonist must be initiated. During the study, periodic drug level monitoring for both bicalutamide and the anastrazole will be performed. To this end, determine plasma levels for both drugs at the following timepoints: predose, trough drug concentrations before the second dose, between days 8 and 14, and at 1 month, 2 months, and 3 months after the first dose. The determination of plasma drug concentrations should allow quick turnaround time for dose adjustment purposes. Every dose adjustment should be followed by trough plasma drug level measurements before the next dose, between days 8 and 14, and at 1 month, 2 months, and 3 months after the dose change. Plasma sampling should be done no sooner than three drug half-lives after dose adjustment. An assessment of the dose and dosing schedule for both drugs will be performed after evaluating the pharmacokinetic information for the first four patients on-treatment. This process will be repeated for additional panels of four patients until an appropriate dose regimen is established.

Age group and number of subjects to be studied:

Studies 1 and 2. Adult volunteers, with 24 volunteers completing each study.

Study 3. Boys - 3 years of age and older, with 12 evaluable patients who have complete efficacy and safety data at the end of one year of treatment.

Entry criteria:

Studies 1 and 2. Healthy, adult, non-smoking volunteers who do not receive any prescription or over-the-counter medications or any dietary supplements.

Study 3. Diagnosis of testotoxicosis confirmed by DNA analysis of peripheral blood samples; no evidence of central precocious puberty as demonstrated by GnRH stimulation test. A minimum of six-months of pre-study growth information (height, height velocity, and bone age) will be available prior to enrollment. Collection of pre-study growth data should meet strict endocrinological standards of accuracy and should be well documented.

Endpoints:

Studies 1 and 2. Bicalutamide and anastrozole pharmacokinetic parameters, such as relative BA, $AUC_{0-\infty}$, AUC_{0-t}, CL/F, V_d/F, C_{max}, T_{max}, λ_z, $t_{1/2}$, and their descriptive statistics should be evaluated.

Study 3. Primary endpoint: change in growth rate after 12-months of treatment relative to the growth rate during the ≥ 6-month pre-study period.

Additional assessments:

Study 3.

- change in growth rate (cm. and standard deviation score) after 6-month of treatment relative to the growth rate during the ≥ 6-month pre-study period
- change in rate of bone age maturation after 6 and 12-month of treatment relative to the rate of bone age maturation during the ≥ 6-month pre-study period (rate of bone age maturation will be defined as interval change in bone age/interval change in chronological age)
- comparison of on-study data with historical data from the referenced study (Lescheck et al.) at the end of one year of treatment for growth rate, bone age maturation, and percentage of patients showing improvement in aggressive behavior and acne lesions
- number and percent of patients who achieve and/or maintain growth rates between the 5^{th} and the 95^{th} percentile
- change in predicted adult height (PAH) at the end of the study compared to baseline PAH
- incidence of patients with breast pain and gynecomastia at the beginning and the end of the trial
- evolution of signs and symptoms of virilization while on study medication (virilization signs and symptoms to be followed are: testicular volume, Tanner staging, number of acne lesions, and aggressive behavior)

- descriptive statistics of the plasma bicalutamide and anastrazole concentrations

Drug information:

Studies 1 and 2:

Dose:	50-mg bicalutamide or 1-mg anastrozole
Dosage form:	liquid (to-be-developed for both test medications) and tablet (for both marketed test medications)
Route of administration:	oral
Regimen:	each subject will receive the liquid and tablet for both test medications
Formulation:	pediatric liquid (to-be-developed for both test medications) and tablet (for both marketed test medications)

Study 3.

Dosage form:	liquid (to be developed)
Route of administration:	oral
Regimen:	bicalutamide will be started at a daily dose of 0.5 to 1 mg/kg and will be titrated to a plasma level in a range of 5 to 15 μg/mL; anastrazole will be started at a daily dose of 0.5 mg and will be titrated with the goal of maintaining normal serum estrogen levels
Formulation:	age appropriate

Use an age-appropriate formulation in the studies described above. Any unapproved formulation will need to be supported by a study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency as part of the response to this Written Request.

Drug-specific safety concerns:

The safety profile of bicalutamide /anastrazole combination in children is not known. To this end, a 3-month juvenile rat toxicity study (males only) of bicalutamide /anastrazole combination will be completed and the results will be presented to the agency for review prior to initiating the clinical study.

During the clinical study, bicalutamide-specific adverse events should be monitored, particularly, hepatic adverse events (e.g., elevated transaminases, jaundice, diarrhea, nausea, vomiting,

asthenia). Anastrazole-specific adverse events identified in the drug label should also be monitored.

***Statistical information*:**

Change in growth rate after 12 months of treatment relative to growth at baseline will be analyzed using a one-sample T-test. A 95% 2-sided confidence interval also will be calculated for the mean change in growth rate. All other endpoints will be summarized using descriptive statistics. Mean changes and individual changes will be presented.

Change in growth rate and rate of bone maturation after 12 months of treatment will be compared with the data generated in the referenced study (Lescheck et al.).

Conduct two sets of analyses: an all-treated analysis, consisting of patients who are treated and have on-treatment data, and a protocol-valid analysis for all patients who adhere to the protocol.

***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.

Although not required at the time of pediatric exclusivity determination, we request that you monitor the study participants until final height is reached in all patients. To this end, submit the information in annual reports. Patients should be monitored with respect to above-listed endpoints/assessments every six to twelve months.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before March 31, 2008. 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 the 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) to the Division of Metabolic and Endocrine Drug Products** 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 Enid Galliers, Chief, Project Management Staff, at 301-827-6429 or Monika Johnson, Regulatory Project Manager, at 301-827-9087.

Sincerely,

{See appended electronic signature page.}

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

4/17/03 05:13:25 PM