



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,138
NDA 20-541

AstraZeneca Pharmaceuticals, LP
Attention: E. Jane Valas, Ph.D.
Associate Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

WRITTEN REQUEST
Amendment # 4

Dear Dr. Valas:

Please refer to your October 28, 2004, correspondence to IND 62,138 requesting changes to FDA's December 19, 2003, Written Request Amendment # 2 (as amended by the unnumbered amendment dated May 7, 2004) for pediatric studies for Arimidex (anastrozole) tablets.

We reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows, with highlighted (**Bold**) text denoting changes. This Written Request supersedes the Written Request dated May 9, 2001, as reissued July 2, 2002, and as amended November 19, 2002 (amendment # 1), December 19, 2003 (amendment # 2), and May 7, 2004 (amendment not numbered).

Type of studies:

- Study 1. A six-month, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of anastrozole in pediatric patients with moderate-to-severe pubertal gynecomastia.
- Study 2. A one-year, open-label, multicenter study to assess the efficacy and safety of anastrozole in pediatric patients with McCune Albright Syndrome (MAS).
- Study 3. A pharmacokinetic (PK) study of anastrozole in male pediatric patients with pubertal gynecomastia.
- Study 4. A PK study in pediatric patients enrolled in Study 2.

Objectives/rationale (indications to be studied):

Study 1. To assess the safety and efficacy of anastrozole in reversing breast development in boys with severe pubertal gynecomastia.

Study 2. To assess the safety and effectiveness of anastrozole in slowing the progression of puberty in girls with gonadotropin-independent precocious puberty due to MAS.

Study 3. Primary: to assess anastrozole PK in boys with pubertal gynecomastia and

Secondary: to explore the effectiveness of anastrozole in reversing breast development in boys with moderate-to-severe pubertal gynecomastia of shorter duration than that evaluated in Study 1.

Study 4. To assess anastrozole PK in patients with MAS.

Study design:

Study 1. A double-blind, randomized, placebo-controlled safety and efficacy study in which boys with gynecomastia will receive anastrozole or placebo for up to six months.

Study 2. An open-label safety and efficacy study in which girls with MAS will receive anastrozole for one year. A six-month observational period prior to study treatment will be included.

Study 3. A 6-month open-label PK and clinical study in boys with pubertal gynecomastia. Serial blood samples must be collected over a 24-hour dosing interval at steady state to assess anastrozole PK.

Study 4. A population pharmacokinetic study in girls enrolled in Study 2; a sparse sampling strategy will be acceptable. For each patient, approximately two blood samples will be collected after the initial dose. The first blood sample will be drawn between the initial dose and 2 hours post-dose (0-2 hr after first dose). The second blood sample will be drawn at any time between 3 hours post the initial dose and before the second dose (i.e., 24 hours). The patient will continue to take anastrozole once every 24 hours after the initial dose. The following should be recorded: time of daily administration, time of blood collection, and time of last dose with respect to collection of each blood sample. Two additional blood samples will be drawn after two weeks of drug treatment for steady-state monitoring. A fixed sampling time should be avoided.

Alternatively, a single-dose population pharmacokinetic study can be conducted in girls enrolled in Study 2. If this is the case, five sparse blood samples each will be needed from approximately 80% of the patients enrolled in Study 2. The first sample will be drawn 0 -- 2 hours post initial dose. The second, third, fourth, and fifth blood samples will be drawn 3 -- 6 hours, 24 -- 30 hours, 45 -- 48 hours, and 72 -- 96 hours post the initial dose, respectively. A fixed time sampling should be avoided. After the pharmacokinetic sampling is complete, the girls will receive anastrozole once every 24 hours for the duration of Study 2.

Age groups in which studies should be performed:

Study 1. Boys ≥ 11 years and ≤ 18 years of age will be enrolled.

Study 2. Girls ≤ 10 years of age will be enrolled.

Study 3. Boys ≥ 11 years and ≤ 18 years of age with pubertal gynecomastia.

Study 4. Girls ≤ 10 years of age will be enrolled.

Number of patients to be studied:

- Study 1. At least 60 boys will be treated for six months.
- Study 2. At least 20 girls will be treated for one year.
- Study 3. 24 boys who complete the study, **with an age distribution of subjects approximately consistent with the age distribution of pubertal gynecomastia within the age group specified above.**
- Study 4. All patients treated in Study 2, if possible, should be enrolled in the population PK study or at least 80% of the patients in Study 2 if you opt for the single-dose population PK study.

Entry criteria:

- Study 1. Boys with pubertal gynecomastia with breast diameter ≥ 3 cm that has not decreased in diameter by ≥ 0.5 cm during three months of clinical observation.
- Study 2. Girls with classical or atypical MAS and progressive precocious puberty manifested by signs of pubertal development, **vaginal bleeding**, and/or significantly advanced bone age (**bone age at least 12 months beyond chronological age at the time of screening.**)
- Study 3. Boys with pubertal gynecomastia with a breast measurement of at least 2 cm in diameter that has not decreased in diameter during 3 months of clinical observation.
- Study 4. Patients enrolled in Study 2.

Study endpoints:

Study 1:

Primary:

A $\geq 50\%$ reduction between visit 1 and end of study in the calculated breast volume (combined) based on ultrasound.

Additional endpoints:

- a) Proportion of patients with $\geq 50\%$ reduction in breast volume by end of study
- b) Actual percent change in breast volume
- c) Change in breast pain in symptomatic patients
- d) Changes in sex steroid and gonadotropin levels
- e) Changes in height
- f) Tolerability and safety

Study 2:

- a) Changes 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).
- b) Proportion of patients with baseline vaginal bleeding who experienced $\geq 50\%$ reduction in the number of vaginal bleeding episodes on treatment.
- c) Proportion of patients with baseline vaginal bleeding who experienced cessation of vaginal bleeding episodes over a 6-month trial period and over the whole 12-month trial.
- d) Change in bone age advancement on treatment compared to change during baseline (provide data for both the 6-month and the 12-month time points).
- e) Change in growth velocity on treatment compared to change during baseline (provide data for both the 6-month and the 12-month time points).

Additional assessments:

- a) Change in Tanner stage (breast and pubic hair) at 12 months relative to baseline
- b) Change in uterine volume at 6 months and 12 months of the trial relative to baseline uterine volume
- c) Change in ovarian volume at 6 months and 12 months of the trial relative to baseline ovarian volume (categorization of the number and size of ovarian cysts should be attempted)
- d) Predicted adult height at 12 months of the trial relative to baseline
- e) Tolerability and safety data

Study 3.

Primary:

PK endpoints such as $C_{ss, \max}$, $C_{ss, \min}$, $t_{\max}$, AUC_{ss} , CL/F , and V_z/F will be determined.

Secondary:

- a) proportion of patients with $\geq 50\%$ reduction in breast volume by end of study
- b) actual percent change in breast volume
- c) change in breast pain in symptomatic patients
- d) change in height
- e) tolerability and safety

Studies 3 and 4

The effects of demographic covariates (e.g., age, body weight, sex) on anastrozole PK in these populations should be analyzed.

Study 4.

PK endpoints such as AUC , $C_{\max}$, $T_{1/2}$, CL/F , and V_{ss}/F will be determined.

Drug information:

<i>dosage form:</i>	tablet
<i>route of administration:</i>	oral
<i>regimen:</i>	dose up to 1 mg/day (Studies 1 and 3); dose up to 10 mg/day (Studies 2 and 4);
<i>formulation:</i>	marketed tablet

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.

Drug-specific safety concerns:

Diarrhea, nausea, vomiting, liver abnormalities.

Statistical information, including power of study and statistical assessments:

Study 1 The proportions of patients achieving the primary endpoint in each treatment group will be compared using the appropriate statistical methods. At least one analysis of the primary endpoint will make use of the intent-to-treat (ITT) population consisting of all randomized subjects with an observation at visit 1 and at least one observation after randomization. Additional endpoints as well as safety will be analyzed descriptively.

Study 2

Paired t tests will be used to compare the 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 95% confidence interval should also be constructed for the mean difference between treatment and baseline. Appropriate nonparametric methods will be used if assumptions for t test are not satisfied. Correlations between growth rate changes and bone age changes should be performed.

Descriptive statistics should be presented for all study end points. Descriptive statistics for continuous variables should include sample size, mean, median, 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.

Study 3

Primary:

Descriptive statistics will be reported for the PK parameters and the effect of covariates on CL/F; V_z/F will be studied using the appropriate statistical methods.

Secondary:

Descriptive analyses for both efficacy and safety endpoints.

Study 4

Descriptive statistics will be reported for the PK parameters and the effect of covariates on CL/F; V_{ss}/F will be studied using the appropriate statistical methods.

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.

Although not required to obtain pediatric exclusivity, we request that you make a commitment to monitor annually the participants in Study 2 until age 12 or until discontinuation of drug and that you submit information in your annual reports. The patients should be monitored with respect to the Study 2 endpoints and the drug safety parameters.

Timeframe for submitting reports of the studies:

Reports of the studies that meet the terms of this Written Request must be submitted to the Agency on or before **October 31, 2007**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. **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.**

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 **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 **IND 62,138**. 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> & <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/>.

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
Offices of 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
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