DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 4

NDA 20-838

AstraZeneca LP
Attention: Ms. Paula R. Clark
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Clark:

Please refer to your correspondences dated October 12, November 9, and December 12 2006, requesting changes to FDA's Written Request for pediatric studies, originally issued March 15, 1999, superseded January 8, 2003, amended May 7 and August 27, 2004, and March 15, 2005, for Atacand (candesartan cilexetil) Tablets.

We have reviewed your proposed changes, and are amending the "Racial groups" subsection to change the racial requirement and the "**Reporting**" section to extend the timeline in your Written Request. All other terms stated in our Written Request issued on January 8, 2003 and all subsequent amendments remain the same.

To obtain needed pediatric information on candesartan cilexetil, 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 trials in pediatric patients as described below:

Strategy

The requested data will provide guidance for the use of candesartan cilexetil to reduce blood pressure in pediatric patients.

These data will be derived from:

- pharmacokinetic sampling in patients spanning the same age range as those to be studied for effectiveness,
- a dose-ranging trial of effectiveness in hypertensive pediatric patients; and
- safety data derived from a controlled trial and a 1-year open treatment phase following the effectiveness trial, and a summary of all available information on the safety of the drug in hypertensive pediatric patients. The safety evaluation in children should include a summary of the published literature and formal analyses of published and unpublished data. Unpublished data should be sought from organizations participating in healthcare delivery to the pediatric population.

Pediatric Subgroups

Age groups

The four pediatric age groups to which we refer in this document are:

- infants and toddlers (age 1 – <2 years),

- pre-school children (age 2 – <6 years),
- school-age children (age 6 – <Tanner stage 3), preferred group for effectiveness study, and
- adolescents (Tanner stage 3 – <17 years).

With respect to effectiveness, studies of antihypertensive drugs should include at least 50% pre-pubertal patients, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults. At least 25% of patients should be infants to pre-school age.

For purposes of antihypertensive drug development, it is useful to divide pediatric patients into "pre-school" and "school-age" patients. School-age children (above the age of approximately 6 years)

- are usually able to swallow solid dosage forms,
- may tolerate doses similar to the smallest doses approved for adults, and
- are fairly often diagnosed with hypertension of no specific cause.

Below this age, formulation issues are more important, and almost all diagnosed hypertension is attributed to renal disease or other specific causes.

Racial groups

Because response to some therapies in adult hypertension appears to be different in black and non-black populations, your recruitment scheme should be designed to assure 35-60% black patients at enrollment.

Formulation Issues

Formulations should be well characterized and appropriate to the age and clinical setting. Any unapproved formulation will need to be supported by a study of the relative bioavailability of candesartan cilexetil; these studies may be conducted in adults. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and you will need to obtain an agreement with the Agency regarding the adequacy of the formulation you use. Full study reports of any relative bioavailability studies should be submitted to the Agency.

Dose-Ranging Trial

Trial design

The dose-ranging study should be double-blind in design and include arms for at least three dose levels of candesartan cilexetil. The doses chosen should result in blood levels that range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the highest approved adult dose[1]. Randomization should be stratified by age and race. The parallel portion of the study should be at least 2 weeks from the titration to target doses. The primary end point should be either absolute or percentage change in systolic or diastolic pressure. You can allocate alpha to each active arm in a placebo-controlled study or look for a positive slope to the dose-response relationship. The primary analysis should include all patients with data on randomized treatment.

[1] *Doses would usually be derived from adult doses scaled by body surface area, but there should be, from pharmacokinetic data, assurance that these doses will in fact place patients in the range of blood levels attained in adults.*

If the pharmacokinetics of the drug in children, derived from the pharmacokinetic trial described below, differ substantially from the reported pharmacokinetics in adults, such that the serum half-life is appreciably altered, the trial should include an assessment of the effect of varying dosing interval on trough antihypertensive effect. This should include measurement of the effects of the drug throughout the dosing interval.

Acceptable options for trial design are as follows:

The most straightforward, acceptable trial (Trial A) would be one in which each patient is randomized to placebo or to one of three doses of study drug.

Although we believe that the hazard associated with two weeks of placebo treatment is likely to be small, we recognize that parents and others may be reluctant to enroll pediatric patients in a traditional placebo-controlled trial. An alternative design (Trial B) would be similar to Trial A, but without the placebo arm.

Patients in Trial C would be recruited and treated like those in Trial B, but, at the end of the 2-week treatment period, patients would be re-randomized in blinded fashion to continue on their assigned treatments or to be withdrawn to placebo. The analysis of Trial C would be a slope analysis for the first phase. If the first phase failed to reveal a statistically significant non-zero slope to the dose-response curve, an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. This design would allow you to distinguish among a significant dose response, doses too low or no effect for some other reason (no slope to dose-response, withdrawal indistinguishable between active treatment and placebo), and doses too high (no slope to dose-response, less withdrawal effect on active treatment).

It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of study drug and then randomly withdrawn to lower doses (including placebo).

Although there may be a placebo group and/or a period of drug withdrawal, the short duration of therapy withdrawal or nonactive treatment should pose no risk so long as patients are appropriately monitored.

Measurement of blood pressure

You should consistently measure both systolic pressure and diastolic pressure in all patients. You should prospectively identify either the systolic or diastolic blood pressure as the primary end point. For the trial designs other than randomized withdrawal from active drug (see above), the primary efficacy measurement should be the change in blood pressure from baseline to the end of the treatment period plus the dosing interval (trough). For randomized withdrawal trial designs, the primary efficacy measurement should be the change in blood pressure from the last on-treatment visit to the end of the withdrawal period.

Recruiting

The trial should be performed in patients of both sexes in one or more of the pediatric age groups defined above, preferably school-age children. If adolescents are included, at least one additional age group must be included, and 50% of the patients in the trial should be <12 years old. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They should not be recruited if other interventions known to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. Patients should be evaluated weekly, so that unacceptable increases in blood pressure can be detected and treated promptly.

Eligibility

Prior treatment with candesartan cilexetil or other therapy should be neither required nor disqualifying. A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient who is receiving antihypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period.

Statistical considerations

The trial should be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance. Submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes.

Interpretability

A successful study ($p<0.05$ for its pre-specified primary end point analysis) is clearly interpretable. An unsuccessful study will be considered interpretable if it demonstrates that the study was powered to find a "clinically meaningful" treatment benefit on blood pressure (change from baseline and placebo) for the highest dose or for all doses combined.

The latter requires you to show by a post-hoc power analysis based on the observed variability, that if the true treatment effect were "clinically meaningful", the 95% confidence interval would have excluded zero treatment effect with ≥90% power. You may wish to obtain an estimate of variability from a preliminary study, or you may obtain a penalty-free estimate of variability from a pooled interim analysis (without unblinding) and then follow a pre-specified rule to adjust the sample size.

For the purpose of satisfying the interpretability criteria of this Written Request, a clinically meaningful treatment benefit is considered to be a 3-mmHg reduction in blood pressure.

Any other unsuccessful result will be considered not interpretable. A study that is not interpretable will be considered not responsive to the Written Request.

Long-term safety

Patients in the trial(s) of clinical efficacy should be enrolled in an open-label follow-on study with safety (adverse events), growth (change in head circumference[2], weight, and length or height), and development (milestones, school performance, or neurocognitive testing) assessed at baseline and at one year.

Pharmacokinetic Trials

Pharmacokinetic data should be obtained from patients with grossly normal metabolic function in the same age range as you study for effectiveness. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters.

In the age group studied in the dose-ranging trial, some or all of the pharmacokinetic data may be obtained from patients in that trial or from safety studies. Data should be collected with respect to candesartan cilexetil and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the exposure (AUC), half-life, oral apparent clearance, volume of distribution, Cmax, and tmax in pediatric subjects of the various age groups.

[2] *Up to age of 3 years.*

These results should be discussed in comparison with results in adults.

Labeling Changes

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Reporting

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.

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format. The submission should include electronic datasets for all clinical trial data for these studies, submitted according to available guidance.

Reports of the above studies must be submitted to the Agency on or before **July 31, 2009**. Remember 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.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be 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. 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.

- *Format of reports to be submitted*: 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 study(s) 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.

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, 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.

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/.

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, please call:

Quynh Nguyen, Pharm.D.
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

Norman Stockbridge

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