



NDA 21-286

Sankyo Pharma, Inc.  
Attention: Mr. Albert S. Yehaskel  
399 Thornall Street  
11<sup>th</sup> Floor  
Edison, NJ 08837

Dear Mr. Yehaskel:

Please refer to our March 6, 2001 Written Request for pediatric studies for Benicar (olmesartan medoxomil) Tablets. We also acknowledge your pediatric-related submission of August 20, 2002 (to IND 47,887).

The Food and Drug Administration (FDA) is hereby amending the Written Request for olmesartan medoxomil, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act (the Act). This Written Request supersedes the March 6, 2001 Written Request and the July 3, 2002 reissue of this Written Request. We request that you submit information from trials in pediatric patients as described below.

### Strategy

The requested data will provide guidance for the use of olmesartan medoxomil 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 the controlled trial(s) 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safety evaluation in children should include a summary of the published literature and formal analyses of published and unpublished data. Unpublished data should be sought from organizations participating in healthcare delivery to the pediatric population.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 40-60% black patients.

### **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 olmesartan medoxomil; 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 olmesartan medoxomil. 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<sup>1</sup>. 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 be intent-to-treat.

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, but then (if the first phase revealed a flat 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 (line not flat), doses too low or no effect for some other reason (line flat, withdrawal identical between active treatment and placebo), and doses too high (line flat, withdrawal slower 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 non-active treatment should pose no risk so long as patients are appropriately monitored.

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<sup>1</sup> 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.

#### Measurement of blood pressure

You should consistently measure both systolic pressure and diastolic pressure in all patients. You should 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. 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 likely 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 followed weekly, so that unacceptable increases in blood pressure can be detected and treated promptly.

#### Eligibility

Prior treatment with olmesartan medoxomil 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 placebo-controlled study will be considered interpretable if it demonstrates that the study was powered to find a "clinically meaningful" treatment benefit on the primary end point. 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  $\geq 90\%$  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 3 mmHg (placebo-subtracted change from baseline) for the highest dose or for all doses combined (and the protocol should specify which of these is to be used). Any other unsuccessful result will be considered not interpretable.

A study that does not include a placebo group is interpretable if it demonstrates a significant ( $p < 0.05$  for its pre-specified primary end point analysis) non-zero slope for the relationship between drug dose and change from baseline in blood pressure.

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<sup>2</sup>, 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 olmesartan medoxomil 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,  $C_{max}$ , and  $t_{max}$  in pediatric subjects of the various age groups.

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**

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 and pharmacokinetic trial data for these studies, submitted according to available guidance.

Reports of the above studies must be submitted to the Agency on or before March 6, 2005. 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.

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. If your pediatric development program differs from the terms of the Written Request, it is your responsibility to seek an amendment to the Written Request or to seek a Written Agreement.

If you wish to discuss any amendments to this Written Request, 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.

Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark such a 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 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 (30) or messenger to:

Director  
Office of Generic Drugs  
HFD-600, Metro Park North II

7500 Standish Place  
Rockville, MD 20855-2773

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 contact:

Mr. Edward Fromm  
Regulatory Health Project Manager  
(301) 594-5332

Sincerely,

Rachel Behrman, M.D., M.P.H.  
Deputy Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
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