



NDA 19-962

AstraZeneca LP
Attention: Ms. Cindy M. Lancaster
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

Reference is made to our December 18, 2002 Written Request for pediatric studies for Toprol-XL, (metoprolol succinate) 50, 100 and 200 mg Extended Release Tablets and to your request of March 26, 2003 to extend the date for final reports. Please note that the following Written Request supersedes that of December 18, 2002, which is no longer valid.

To obtain needed pediatric information on metoprolol succinate, 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 trials in pediatric patients described below.

Strategy

The requested data will provide guidance for the use of metoprolol succinate 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 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safety evaluation in children must include a summary of the published literature and formal analyses of published and unpublished data. Unpublished data may be obtainable from organizations participating in healthcare delivery to the pediatric population.

Although not a part of this Written Request, we remind you that it may be important to determine the effect of metoprolol succinate on the growth and development of pediatric patients, and we encourage you to perform an active control comparison with diuretic-based therapy.

Pediatric Subgroups

Age groups

The five pediatric age groups that we refer to in this document are:

- neonates (age less than one month),

- infants and toddlers (age 1 - 24 months),
- pre-school children (age 2 - 6 years),
- school-age children (age 6 – 12 years or \leq Tanner Stage 3), preferred group for effectiveness study, and
- adolescents (> 12 years or $>$ Tanner Stage 3 - 16 years).

With respect to effectiveness, studies of antihypertensive drugs should be focused on, and include a reasonable proportion of, pre-pubertal children, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults.

For purposes of antihypertensive drug development, it is useful to divide “children” into “pre-school ”and “school-age” children. 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 a mixture of black and non-black patients.

Formulation Issues

Formulations must 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 metoprolol; 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

A trial that would be considered responsive to this request will entail randomized, double-blind observation of parallel dose groups, using a population judged to be of adequate size on the basis of realistic estimates of effect size and the usual statistical calculations. The trial need not be successful (that is, it need not demonstrate that any particular regimen of metoprolol succinate is effective in pediatric patients), but it must be interpretable, as explained in the following discussion of possible study designs.

The most straight-forward, acceptable trial (Trial A), would be one in which each patient is randomized to placebo or to one of three different doses of metoprolol succinate, with the doses chosen to give blood levels in a 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 After two weeks of treatment,² the trial would be analyzed by looking for a

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

² The study period might need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose.³ If the slope of this line were not differentiable from zero, the trial would be unsuccessful by our usual criteria (i.e., it would show no effect), but it would be interpretable.

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.

If analysis of Trial B revealed a significantly positive slope to the dose-response line, the trial would be considered successful by the usual criteria. If, however, Trial B, shows no dose-response, i.e., if the dose-response line is horizontal, the trial will be considered uninterpretable, not merely unsuccessful.⁴ In this case, Trial B would then be considered not responsive to this request.

To avoid this possibility, Trial B could be modified to include a randomized withdrawal phase (Trial C). Patients in Trial C would be recruited and treated like those in Trial B. At the end of the 2-week treatment period, patients would be rerandomized in blinded fashion to continue on their assigned treatments or to be withdrawn to placebo, with close follow-up and withdrawal to open-label treatment at the discretion of their physicians. 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 positive 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). Because this is essentially a placebo-controlled trial, it would be considered interpretable no matter what the outcome so long as the sample size for the withdrawal phase were adequate.

It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of metoprolol succinate and then randomly withdrawn to lower doses (including placebo), with the same close follow-up, discretionary withdrawal to open-label therapy, and analysis as in Trial C.

Recruiting

The trial must 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 also be included, and at least 50% of the patients in the trial should be 6 – 12 years old or \leq Tanner Stage 3 or younger. 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 must 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 promptly and treated.

Eligibility

Prior treatment with metoprolol succinate 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 hypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period. 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.

³ In general, there will be interest in the effect on both systolic and diastolic pressure. Usually, the best measure of blood pressure change will be mmHg, but if pressures vary widely, percent change could be used.

⁴ When placebo is included (as in Trial A), a flat dose-response line means simply that all of the doses tested were too low, so they were ineffective, or that the drug does not work in children. Without placebo (as in Trial B), it is alternatively possible that all of the doses tested were too high, and that they were all equally effective.

You should take steps to attempt to obtain a reasonable distribution of age, race, and gender in the trial.

Duration

The study period should generally be of two weeks duration; it may need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

Statistical considerations

The trial should be designed with at least 80% power to detect a treatment effect of conventional ($P= 0.05$) statistical significance. Please 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. It may be useful to make some groups larger to obtain additional safety information, or allow better assessment of subgroups.

Pharmacokinetic Trials

Pharmacokinetic data must be obtained over the range of ages studied for clinical effectiveness. Patients must have grossly normal metabolic function. 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 must be collected with respect to metoprolol and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected must 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

The results of the completed studies may be used in the labeling of your drug product to add information allowing proper dosing for the safe and effective use for the reduction of blood pressure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population⁵ that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your product is approved.

Reporting

Full study reports of the requested trials, including full analysis, assessment, and interpretation, must be submitted in the usual format. All data should be submitted in machine-readable form according to applicable guidance.

Reports of the above studies must be submitted to the Agency on or before October 19, 2006. Please remember that pediatric exclusivity only adds 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.

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 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 must be submitted as a supplement to your approved NDA with the proposed labeling changes

⁵ For example, pediatric patients with hypertension secondary to advanced renal disease.

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. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

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 to the pediatric population.

If you have any questions, please contact:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

(electronic signature appended)

Rachel Behrman, M.D.
Deputy Director
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/

Rachel Behrman
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