U.S. Food and Drug Administration
Center for Drug Evaluation and Research

Sample Written Request for Oral Antihypertensives

This is a sample Written Request outlining the pediatric studies the Agency believes will provide a meaningful health benefit to the pediatric population for oral antihypertensives. An actual Written Request may differ from this sample depending upon the nature of the specific drug product and any other indications for which it is used. To receive a formal Written Request for pediatric studies under section 505A of the Federal Food, Drug, and Cosmetic Act for a particular oral antihypertensive agent, please submit a proposed pediatric study request to the Division of Cardio-Renal Drug Products. The proposed pediatric study request should incorporate the material in this sample and include descriptions of any other studies necessary to provide a meaningful health benefit to pediatric populations. Please refer to the outline in the "Guidance For Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act," for additional information.

To obtain needed pediatric information on generic drug name, 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 generic drug name to reduce blood pressure in pediatric patients. These data will be derived from

- a dose-ranging trial in hypertensive pediatric patients;
- pharmacokinetic trials in subjects from four pediatric age groups: infants and toddlers, pre-school children, school-age children, and adolescents; and
- safety data derived from the controlled trial and an open treatment phase following the trial, with a summary of all available information on the safety of the drug in pediatric patients.

Although not a part of this Written Request, we remind you that it may be important to determine the effect of generic drug name 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 --Tanner Stage 3), preferred group for effectiveness study, and
- adolescents (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

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if standardized, palatable, and shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailablility compared to the marketed product.

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 generic drug name 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 generic drug name, 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. After two weeks of treatment, the trial would be analyzed by looking for a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose. 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. 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 followup 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 generic drug name and then randomly withdrawn to lower doses (including placebo), with the same close followup, discretionary withdrawal to open-label therapy, and analysis as in Trial C.

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 also be included, and 50% of the patients in the trial should be 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 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 promptly. Prior treatment

with generic drug name or other therapy should be neither required nor disqualifying.

Eligibility

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.

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 to allow better assessment of subgroups.

Pharmacokinetic Trials

Pharmacokinetic data should be obtained from subjects with grossly normal metabolic function from infants and toddlers, pre-school children, school-age children, and adolescents. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters. A draft guidance document on pediatric pharmacokinetic studies is available [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].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 generic drug name 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 bioavailability (AUC), half-life, C_{max} , and t_{max} in pediatric subjects of the various age groups.

Format of Reports

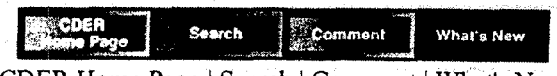
Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format; or, as an alternative, you may submit an abbreviated study report along with all data in electronic form, with a case report form annotated with the names of the SAS variables used for each blank on the form.**Labeling**

Changes

The results of the completed studies may be used in the labeling of your drug product(s) 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 population that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your product(s) is/are approved.

Timing of Submission of Reports

Reports of the above studies must be submitted to the Agency on or before two years from the date of this letter. 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.



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