DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-437
IND 51,780

G.D. Searle LLC
c/o Pfizer, Inc.
Attention: Andrea Kollath, D.V.M.
4901 Searle Parkway
Skokie, IL 60077

Dear Dr. Kollath:

Please refer to your correspondence dated May 4, 2006, requesting changes to FDA's October 1, 2004 amended Written Request for pediatric studies for Inspra® (eplerenone) 25, 50 and 100 mg Tablets.

Reference is also made to the Pediatric Written Requests for studies of eplerenone issued August 17, 2000 and July 2, 2002 following the enactment of the Best Pharmaceuticals for Children Act.

We refer to your amendments dated October 13, 2000, May 14, 2001, and February 6, 2003 that provide for an amended pediatric protocol, your request for an amended Written Request with an extension beyond the August 17, 2004 deadline, and to a teleconference between the Division and you on March 6, 2003 regarding the proposed amended pediatric protocol.

We have reviewed your proposed changes and are amending the below-listed section of the Written Request in recognition of the difficulty you have experienced in recruiting African-American subjects. All other terms stated in our amended Written Request issued on October 1, 2004 remain the same.

This Pediatric Written Request includes the following change:

From:
Racial groups
Because response to some therapies in adult hypertension appears to be different in black and non-black populations, if you study a general hypertensive population in children, your recruitment scheme must result in 40-60% black patients at enrollment.

To:
Racial groups
Because response to some therapies in adult hypertension appears to be different in black and non-black populations, if you study a general hypertensive population in children, your recruitment scheme must result in no less than 25% black patients at enrollment.

Revised Pediatric Written Request:
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), to obtain needed pediatric information for eplerenone. This Written Request supersedes the requests issued August 17, 2000 and July 2, 2002. We request that you submit information from trials in pediatric patients as described below. Some of the changes include:
Pharmacokinetic data are requested only for the age group studied for effectiveness.
Specific requirements are set for age and race distributions.
Specific requirements are set for the formulation.
Specific criteria are set for the interpretability of unsuccessful studies.

Strategy
The requested data will provide guidance for the use of eplerenone 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 trial, with 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.

Pediatric Subgroups

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

- neonates (age less than one month),
- 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 must 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. 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, if you study a general hypertensive population in children, your recruitment scheme must result in no less than 25% black patients at enrollment.

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 eplerenone; 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 must be submitted to the Agency.

Dose-Ranging Trial

Trial design

The dose-ranging study must be double-blind in design and it must evaluate at least three dose levels of eplerenone. 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 duration of the parallel portion of the study must be at least 2 weeks from the titration to target doses. The primary end point must be either absolute or percentage change in systolic or diastolic pressure. You can allocate alpha to each active arm in the placebo-controlled comparison or look for a positive slope to the dose-response relationship. The primary analysis must include all patients with data on randomized treatment.

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, 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, withdrawal identical between active treatment and placebo), and doses too high (no slope, 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.

Measurement of blood pressure

You must consistently measure both systolic pressure and diastolic pressure in all patients. You must 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 must be the change in blood pressure from baseline to the end of the treatment period plus the inter-dosing interval (trough). For randomized withdrawal trial designs, the primary efficacy measurement must be the change in blood pressure from the last on-treatment visit to the end of the withdrawal period.

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 50% of the patients in the trial must 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

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[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.*

blood pressure. They must 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 promptly and treated.

Eligibility

Prior treatment with eplerenone 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 must 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 must be obtained over the range of doses studied for effectiveness. Patients must have grossly normal metabolic function. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters.

Data must be collected with respect to eplerenone 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.

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

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, must be submitted in the usual format. 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.

Reports of the above studies must be submitted to the Agency on or before 17 August 2006. 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. You should identify any discrepancies between your proposed protocol and the Written Request. If there are differences, it is your responsibility to seek an amendment to the Written Request or to seek a Written Agreement.

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 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:

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, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request must 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, contact:

Ms. Alisea Sermon, Pharm.D.
Regulatory Health Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
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/

Robert Temple

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