



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Center for Drug Evaluation and Research  
Food and Drug Administration  
Rockville MD 20857

To obtain needed pediatric information on the use of hydrochlorothiazide 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 that you submit information from studies in pediatric patients described below.

**Strategy:**

The requested data will provide guidance for the use of hydrochlorothiazide monotherapy or as add-on therapy to reduce blood pressure in pediatric patients. These data will be derived from:

- Placebo-controlled, randomized, parallel, double-blind, dose-ranging trial with the randomized phase of 4-6 weeks duration to evaluate the effectiveness and safety of hydrochlorothiazide in hypertensive pediatric patients.
- Open-label treatment study of 12 months duration to evaluate the safety of chronic treatment.
- Placebo-controlled, double-blind, randomized two week withdrawal trial of responders from the open-label treatment study.
- Pharmacokinetics (PK) of hydrochlorothiazide in children must be determined from the dose-ranging study. PK-pharmacodynamic (PD) correlations must be performed.

In addition to the safety data from the above studies, a summary and formal analysis of published literature must be submitted. Unpublished data on the use of hydrochlorothiazide in hypertensive children should be sought from organizations participating in healthcare delivery to the pediatric population and also submitted.

The protocols for the dose-ranging trial, the open-label treatment phase, and the placebo-controlled randomized withdrawal trial will be submitted to the FDA and agreed upon prior to study initiation.

**Pediatric Age groups:**

The two pediatric age groups referred to in this document are:

- Pre-Adolescent (6 years to < Tanner Stage 3).
- Adolescent ( $\geq$ Tanner Stage 3 to < 17 years).

Studies of antihypertensive drugs must include at least 50% pre-adolescent patients. The patients within each age group (pre-adolescent and adolescent) should have adequate representation throughout the age range. If the respondent is unable to meet the minimum enrollment requirement for pre-adolescents, the respondent must document the efforts made and consult with the FDA about modification of this enrollment requirement.

**Formulation:**

Age-appropriate formulations must be used in the studies described in this written request. If there is no oral suspension/solution available bioequivalent to the approved form, a solid dosage form suspended in food could be used if it is standardized, palatable and stable and has been shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailability compared to the marketed product.

**Number of Patients:**

The placebo-controlled, parallel group, randomized, double-blind, dose-ranging study must randomize at least 90 patients per treatment group. The long term open-label safety study must have at least 180 evaluable patients (out of the  $\geq 360$  subjects enrolled into the placebo or treatment groups during the double blind, dose ranging study) who either complete one year of therapy or discontinue prematurely for adverse events. The randomized withdrawal portion of the open-label study must enroll a sufficient number of patients to detect a 5 mm Hg difference in standardized systolic blood pressure between the hydrochlorothiazide and placebo groups during the drug withdrawal period (estimate 180 patients).

**Enrollment:**

The protocol must include a validated method of measuring blood pressure for enrollment of patients. Auscultatory blood pressure measurements are preferred.

The trial must be performed in patients of both sexes in the pediatric age groups defined above. Study sites should be selected to ensure enrollment of a diverse population into the proposed trials.

The protocol must define the criteria for screening pre-adolescents for secondary hypertension prior to enrollment.

**Inclusion Criteria:**

Both obese and non-obese patients can be enrolled and randomized if:

- The average of their blood pressure measurements taken over three separate visits is greater than or equal to 95th percentile for age and height or greater than 90th percentile with concurrent conditions, as defined in the “The Fourth Report on the

Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents” (for example, diabetes or evidence of hypertensive target organ damage).

- They have a history of three documented elevated blood pressures that meet the above inclusion criteria, provided the patient can be safely withdrawn from current antihypertensive therapy.

Prior treatment with hydrochlorothiazide or other antihypertensive therapies should be neither required nor disqualifying, provided that the antihypertensive therapy can be adequately washed-out prior to enrollment.

#### **Exclusion Criteria:**

Each of the protocols must define criteria for exclusion of patients with unstable blood pressure or those who are unable to tolerate changes to their antihypertensive regimen. Pediatric patients must not be recruited if procedures known to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial. Patients with secondary hypertension due to Cushing’s syndrome, pheochromocytoma, cardiac disease, and hyperthyroidism must be excluded. Patients with evidence of significant renal dysfunction (e.g. anuria, oliguria or creatinine greater than or equal to two times the upper limit of normal), moderate to severe hepatic impairment; or use of lithium therapy must also be excluded.

#### **Trial Design:**

##### **Lead-in period and enrollment:**

The protocol must specify a lead-in period that will allow for stabilization of blood pressure for those patients in a weight loss program and/or for wash-out of prior antihypertensive therapy. Weight loss interventions will be continued into the placebo controlled dose-ranging trial for patients who meet inclusion criteria. Following the lead-in period, all patients must have their blood pressure measured on three separate occasions to determine if they meet inclusion criteria.

##### **Placebo-controlled, Parallel-group, Randomized, Double-Blind, Dose-Ranging Trial:**

Randomization for the study must be stratified by pediatric age groups. In addition, randomization must also be stratified by either body mass index (BMI) or concomitant use of other antihypertensives in the study but not necessarily both. Investigator must justify criteria for the stratifications used in the study. At the time of randomization, baseline blood pressure measurements will be taken. These measurements are distinct from the three blood pressure measurements used to determine eligibility. The respondent must stipulate the process for determination of baseline blood pressure. This process must be based on the utilization of at least two measurements and should be done at the same time of the same time of the day as will be done for blood pressure effects.

The blood pressures taken to define baseline measurement need not meet the eligibility criteria.

Based on past clinical experience in pediatric patients, the respondent must justify the range of doses to be used to fully capture the therapeutic range of the drug. This study must evaluate at least three dose levels of hydrochlorothiazide. The doses chosen must result in blood levels that range from less than those achieved by the lowest approved adult dose to more than those achieved by the highest generally-used adult dose. The doses selected must be based on mg/kg or body surface area for all enrollees and should exceed 37.5 mg daily (0.54 mg/kg once daily based on a 70 kg adult).

The primary end point must be absolute change in systolic blood pressure. It is recommended that blood pressure both in the sitting and standing position be measured. The respondent must measure the blood pressure effect at the interdosing interval. The trough measurement of systolic blood pressure must be the primary endpoint in this study.

If life-style alterations were begun prior to enrollment, study patients must be urged to continue their standardized non-pharmacological life style alteration program throughout the study.

#### **Open-Label Treatment Phase:**

Following the dose-ranging trial (described above), patients, independent of their blinded therapy, may be continued into the open-label treatment phase for a period of 12 months. New patients who have not participated in the dose-ranging study may be enrolled directly in the open-label treatment phase. The primary goal of this phase will be to assess the safety of chronic hydrochlorothiazide treatment in children. This chronic treatment phase will also be used to determine if the blood pressure effect of hydrochlorothiazide persists during chronic therapy. The protocol must specify and justify how the dose regimen for hydrochlorothiazide will be selected for this open-label phase as well as the type and frequency of safety monitoring.

#### **Placebo-controlled, Randomized, Double-blind Withdrawal Study:**

Following the open-treatment phase, patients who respond to hydrochlorothiazide as specified in the protocol will be continued into a placebo-controlled randomized double-blind withdrawal study of 2 weeks duration. The patients will be randomized to either continuation of their ongoing dose of hydrochlorothiazide or to equivalent placebo.

#### **Measurement of vital signs (blood pressure and heart rate) for all studies:**

The respondent must measure both systolic and diastolic blood pressures and heart rate in all patients using a method standardized for the study. The respondent is encouraged to prespecify the methodology that will minimize variance in blood pressure measurements.

#### **Pharmacokinetics/Pharmacodynamics:**

In regard to PK, the respondent may choose to perform traditional or sparse sampling to estimate PK parameters provided that the PK profile of the drug is fully characterized. Data collected must be used to calculate and estimate the following PK parameters: exposure (AUC), half-life, oral apparent clearance, volume of distribution, C<sub>max</sub>, and T<sub>max</sub> in pediatric patients of the two age groups. The respondent must analyze the PK information and should define a PK-PD model for treatment effect.

**Statistical considerations:**

The dose-ranging trial must be designed to have at least 80% power to find a dose with an effect of 5 mm Hg of conventional statistical significance ( $p < 0.05$ , two-sided) in systolic blood pressure. The statistical analysis plan should be agreed upon with the Agency before the start of the study. The primary analysis must include all patients with data on randomized treatment. The placebo-controlled randomized double blind withdrawal study must have 80% power to detect a 5 mmHg difference between drug and placebo in systolic blood pressure. The proposed statistical analyses plan must be submitted as part of the protocol. Any amendments to the statistical plan must be submitted to the IND with appropriate justification.

**Safety:**

Safety assessments must track the occurrence of adverse events (AEs), including: hypersensitivity (including anaphylaxis), dehydration (postural hypotension), electrolyte disturbances (e.g. hyponatremia, hypochloremic alkalosis, hypokalemia, and hypercalcemia), hyperuricemia (gout), hyperlipidemia, and hyperglycemia. Vital signs, including heart rate, blood pressure, and respiratory rate must be obtained, as must standard laboratory assessments of hematologic, liver, and renal function; and electrocardiogram (ECG). AEs must be followed to their resolution or stabilization.

Criteria for withdrawal of individual patients must be defined in the protocol. An independent Data Monitoring Committee (DMC) must be established for these studies. The study stopping rules used by the DMC must be specified in the protocol.

**Safety assessments during the double-blind, dose-ranging trial:**

During the placebo-controlled, parallel-group, double-blind, dose-ranging trial, safety assessments must be obtained weekly or bi-weekly. ECG assessments as well as vital signs should be collected at a consistent time after dosing. If a serious adverse event occurs, the investigator should obtain a hydrochlorothiazide blood level as soon as possible to help determine if there is a relationship between serum levels and a given AE.

**Safety assessments during the open-labeled follow-up study:**

Patients in the placebo-controlled, randomized, double-blind, dose-ranging trial should be enrolled in a 12 month open-labeled follow-up study. Vital signs and assessment of adverse events must be obtained bi-weekly until blood pressure stabilization and then

every 3 months for the duration of the study. Standard lab assessments should be done every three months and for diabetic patients must include hemoglobin A1C.

**Safety assessments during the randomized, double-blind withdrawal study:**

During the placebo-controlled, randomized, double-blind withdrawal study, vital signs must be obtained weekly and safety assessments will be obtained at the end of the withdrawal study.

**Long-term safety (all studies):**

Long term safety assessments must include growth (change in weight, and height), and development (school performance and/or other age-appropriate assessment tools) assessed at baseline (first entry into the double-blind, dose-ranging trial or the open-labeled follow-up study) and at study completion.

**Drug -Specific Safety Concerns (all studies):**

This product is a sulfonamide-derived drug and must not be used in patients who are sensitive to this drug class. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

**Labeling that may result from these studies:**

Appropriate sections of the label may be changed to incorporate the findings of the studies performed in response to this written request.

**Format of reports to be submitted:**

You must submit full study reports, not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation. 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. 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 (ies) 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.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at <http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf> and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human

Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at <http://www.fda.gov/oc/et/guidance/676661.pdf>.

### **Timeframe for submitting reports of the study (ies)**

Reports of the above studies must be submitted to the Agency on or before 30 June 2012. 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

### **Response to Written Request:**

As per the Best Pharmaceuticals for Children Act, section 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST**" in large, bold type at the beginning of the cover letter of the submission. Please 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, bold type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS -COMPLETE RESPONSE TO WRITTEN REQUEST**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

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/Summary\\_review.htm](http://www.fda.gov/cder/pediatric/Summary_review.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 in the pediatric population.

If you have any questions, call Denise Pica-Branco, Ph.D., Project Manager, at 301-796-1732.

Sincerely,

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