

September 30, 2003

Dear:

To obtain needed pediatric information on this active moiety, 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 studies in pediatric patients described below. These studies investigate the use of baclofen for management of spasticity in pediatric patients.

Background:

Oral baclofen is commonly used to treat spasticity in pediatric patients but there is incomplete information available about dosing, pharmacokinetic parameters (PK), effectiveness, and safety of this drug in children.

Type of Studies:

Study 1: Pediatric Pharmacokinetic-Pharmacodynamic (PK/PD) and Tolerability Study

Study 2: Pediatric Efficacy and Safety Study

Study 3: Pediatric One Year Safety Study

Objectives of Studies:

1. To determine the pharmacokinetics of oral baclofen in pediatric patients and investigate the relationship between plasma concentrations of baclofen and clinical measures of spasticity
2. To determine the optimal dosage range and interval for administration of oral baclofen
3. To evaluate the safety and efficacy of oral baclofen
4. To monitor for the occurrence of pharmacological withdrawal symptoms associated with drug discontinuation and determine methods for safe weaning of drug
5. To examine long-term effects of oral baclofen on neurodevelopmental outcomes

Study Design

Pediatric Pharmacokinetic-Pharmacodynamic (PK/PD) and Tolerability Study

Pharmacokinetic-pharmacodynamic data must be obtained to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data must come from a traditional multiple dose PK study that explores the range of tolerated doses. Because baclofen is typically titrated to clinical effect, we recommend that this study evaluate several tiered dosage groups that are age and weight appropriate and span the expected effective pediatric dose range. Assessments of spasticity must be recorded at appropriate intervals to permit PK/PD correlation. The results of this study must be used to select doses for the efficacy trial.

Pediatric Efficacy and Safety Study

This study must consist of a randomized, double-blind, adequately controlled (e.g. placebo, dose response, or active control) assessor masked, parallel, superiority study with a recommended duration of 8-12 weeks in baclofen naïve patients. The standard of care for this patient population is physical therapy. All enrolled patients, irrespective of study design, must be required to undergo a standardized regimen of physical therapy. Dose selection must be based upon results of the PK/PD and Tolerability study. Safety data must be collected in

the controlled efficacy trial. Patients who withdraw from the trial early or discontinue drug at the end of the study must be assessed for withdrawal symptoms for a minimum of two weeks.

Pediatric One Year Safety Study

Data assessing safety for a minimum duration of 12 months exposure to the drug must be collected. These data could come from open studies, e.g., a longer-term open extension of the controlled efficacy trial populations, from separate longer-term open safety studies, or from controlled studies, e.g., a longer-term safety and efficacy trial. The safety data must be documented at or above the dose or doses identified as effective in an adequately designed trial, as described above. If an adequately designed and conducted efficacy trial fails to detect a drug effect, one year safety data must still be collected, at doses at least as high as the doses typically used in treating patients with this drug. Patients can be eligible for enrollment in the one year safety study even if they have not participated in the pediatric efficacy study.

A patient registry should be established in order to facilitate future patient contact.

Age Groups to be Studied:

Pediatric Patients

1. ≥ 2 years to < 6 years
2. ≥ 6 years to < 12 years
3. ≥ 12 to < 16 years

Number of Patients:

A sufficient number of patients of both sexes to detect a clinically meaningful treatment effect must complete the studies. Pediatric patients must be approximately evenly distributed between sexes. There must be reasonably equal numbers of patients in the age groups and patients must be reasonably distributed within the age ranges and race/ethnic groups.

Study 1: There must be a sufficient number of patients, minimum of 24 (e.g., 8 patients per age group), to characterize pharmacokinetics.

Study 2: The study must be designed to provide at least 80% statistical power to detect a clinically meaningful treatment effect on the primary endpoint.

Study 3: At least 100 patients exposed to drug at clinically relevant doses for at least 12 months is a minimum requirement for assessment of longer-term safety. Consent must be obtained to allow future contact for patient follow-up.

Entry Criteria:

The protocol(s) must include a valid and reliable diagnostic method for recruiting and enrolling children with mild to moderate spasticity resulting from cerebral palsy. The predominant component of the patient's cerebral palsy must be spasticity for enrollment in these trials.

Pediatric patients who have: a history of hypersensitivity to baclofen; impaired renal or hepatic function; or proven gastric dysmotility will be excluded from the studies. Patients who are pregnant or who are sexually active and not using an adequate method of birth control must also be excluded from enrollment.

For the one year safety study, if applicable, the protocol must address the use of concomitant anti-spasticity medications (local or systemic) and adequately control for these factors.

Patient Evaluations and Study Endpoints:

1. Pediatric Pharmacokinetic-Pharmacodynamic (PK/PD) and Tolerability Study:

Appropriate PK parameters such as T_{max} , $t_{1/2}$, C_{max} , AUC_{0-t} , AUC_{0-inf} , K_e (elimination rate constant), apparent V_d (volume of distribution), and apparent oral clearance, as defined by fraction of bioavailable oral dose F , i.e., Cl/F must be calculated. Adequate rationale for not evaluating any of the aforementioned PK parameters must be provided in the protocol. Patients for PK evaluation should be representative of the larger study population with respect to age and gender. Assessments of spasticity will be recorded at appropriate intervals for PK/PD correlation.

2. Pediatric Efficacy and Safety Study:

An instrument specific to spasticity and sensitive to the effects of drug treatment of spasticity in the target population must be used. The choice of the primary assessment instrument and the primary outcome must be justified. It is essential to identify a primary outcome (or outcomes if more than one is considered important) for the controlled efficacy trial; ordinarily, for spasticity, this would be change from baseline to endpoint using an appropriate spasticity scale. Additional age-appropriate assessments must include evaluation of range of motion, pain, frequency and severity of spasms, and should include quality of life and activities of daily living measures.

3. Pediatric Short and Longer-Term Safety:

Routine safety assessments must be collected at baseline and protocol-specified follow-up times, i.e., vital signs, weight, height, clinical laboratory measures, and monitoring for adverse events associated with drug administration or withdrawal (including sedation, respiratory depression, bradycardia, hypotension, decreased GI motility, and seizures).

Neurological, behavioral, and neurocognitive developmental outcomes as assessed by pre-specified and validated age appropriate instruments must be utilized to assess long-term follow up.

At least 100 patients exposed to drug for at least 12 months is a minimum requirement for longer-term safety.

Statistical Information, Including Power of Study and Statistical Assessments:

These studies must have a pre-specified detailed statistical analysis plan appropriate to the study design and outcome measures. Randomization should be stratified with respect to the three specified age groups. The studies must be designed to provide at least 80% statistical power to detect a clinically meaningful treatment effect on the primary endpoint, at a conventional statistical significance (two sided, $p=0.05$). The demographic and safety data will be tabulated and descriptive analysis of safety data will be provided. Descriptive analysis of the PK data must also be provided. A clinically meaningful effect size will be prespecified and justified in the protocol, and will be discussed with the FDA and agreed upon prior to initiating studies.

Drug Information

Dosage form: Age appropriate baclofen preparation

Bioavailability and bioequivalence studies must be performed if an extemporaneous formulation using standardized diluents (e.g. crushed tablets in a slurry) is developed.

Route of administration: Oral

All studies must document the use of adjunct therapies to treat spasticity (i.e. physical/occupational therapy, bracing, etc.).

Individual study discontinuation criteria should be specified in protocols submitted for all studies.

Labeling that may result from the studies: Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. Pharmacokinetic study reports should include analytical method and assay validation, individual drug and/or metabolite concentration-time data and individual pharmacokinetic parameters (and PD data when available). 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(s) must 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 must be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before June 30, 2007. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the 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 NIH.

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. 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 font, bolded 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 – 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 the 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

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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 in the pediatric population.

If you have any questions, call Kristin Phucas, Project Specialist, at 301-827-7777.

Sincerely,

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug
Development
Center for Drug Evaluation and Research