DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Dear Dr.

As per the Best Pharmaceuticals for Children Act, to obtain pediatric information on the use of lithium, 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.

Background

Lithium is often a first line treatment for bipolar disorder, which is a significant problem in children. However, information regarding dosing, pharmacokinetic parameters, effectiveness, and safety of this drug in children and adolescents is incomplete. In 2002, a consensus conference about the methodological issues and controversies in clinical trials for bipolar disease addressed clinical trial design in this population. Representatives from industry, researchers, regulatory staff, family advocates, and clinicians achieved consensus regarding several key elements of clinical trial design in this population. The conference concluded that "methodologically rigorous, large scale clinical trials of treatment of acute mania are urgently needed to provide information regarding the safety and efficacy, in youth, of diverse agents with potential mood-stabilizing properties." The group developed specific recommendations regarding: "inclusion/exclusion criteria, investigator training needs and site selection, assessment and outcome measures, protocol design and ethical issues unique to trials involving children/adolescents, and regulatory agency perspectives." These recommendations were summarized in a report in the January 2003 issue of the *Journal of Child and Adolescent Psychopharmacology.*

Specific Study Requirements for Development Program in Pediatric Mania in Association with Bipolar Disorder

Types of Studies

Pediatric Pharmacokinetic and Tolerability Study (Study I)
Pediatric Efficacy and Safety Study with a subgroup for long-term pharmacokinetic assessments (Study II)
Pediatric Long-term Safety Study (Study III)

The pharmacokinetic and tolerability study will be performed first and results submitted to and assessed by FDA prior to proceeding with the next study(ies). Results from the tolerability study will be used in planning the efficacy and safety study(ies).

Objective/Rationale:

1. To examine the pharmacokinetics of lithium in pediatric patients and develop a dosing schedule which achieves target serum levels while minimizing toxicity in acute mania.
2. To assess the efficacy and safety of lithium in acute mania and obtain long-term pharmacokinetic information.
3. To evaluate the safety of lithium, particularly in regard to short and long-term effects on cognition, growth, thyroid, and renal function.

Study Design:

- Pediatric Pharmacokinetic and Tolerability Study (Study I)

You will perform tolerability studies (in which kinetic data can be obtained) to fully explore the range of tolerated doses before conducting the definitive safety and efficacy studies.

You will obtain pharmacokinetic data to provide information pertinent to lithium dosing in the appropriate pediatric population. Serial blood samples will be collected for pharmacokinetic characterization after the first dose (Day 1) and after the highest tolerated dose for three consecutive doses prior to administration of the morning dose. Lithium is typically individually titrated to a targeted serum level to avoid toxicity. We recommend that this study explore several titration schemes to achieve an optimal tolerated dose. The results of this study must be used to select doses for the efficacy trial.

- Pediatric Efficacy and Safety Study with pharmacokinetic assessments (Study II)

For the controlled efficacy study, you will conduct a randomized, double blind, parallel group, placebo-controlled acute trial, with a minimum duration of 6-8 weeks. In order to allow patients to remain in the acute study, benzodiazepines may be offered when necessary to control acute symptoms.

Additionally, as part of these trials, weekly blood samples pre-morning dose (trough) will be collected from all the patients. A random subset of approximately 24 patients ("the subset group") will have serial sampling weekly (e.g. at 12-, 16- and 24 hours post morning dose).

In addition, although not required as part of this written request, you are strongly encouraged to perform a longer-term efficacy trial. In this randomized withdrawal trial, responders to acute treatment would be randomized to lithium or placebo, with follow-up observation for a period of 6 months or more. Outcomes to be followed include length of time to relapse and treatment of relapsed patients. The protocol for the longer-term efficacy trial will address the handling of other psychotropic agents (e.g. stimulants, benzodiazepines).

The trials will allow for early withdrawal, i.e., treatment with active medications, for patients whose symptoms are not controlled to a specific extent on assigned treatment or who deteriorate. All patients will be offered a standardized psychosocial treatment, e.g. family centered psychotherapy or cognitive behavioral therapy. A Data Safety Monitoring Board will oversee each trial to ensure that the trial is conducted safely.

intolerance, diabetes mellitus or renal dysfunction will also be excluded from the trial. Female adolescent patients must have negative pregnancy tests at onset of trial.

Patient Evaluations and Study Endpoints:

- Pharmacokinetic and Pharmacodynamic Assessments (Studies I and II):

Serum lithium concentrations will be measured for determination of lithium pharmacokinetic parameters such as area-under serum lithium concentration-time curves (AUC), half-life (if possible), apparent clearance, apparent volume of distribution, C_{max}, and t_{max} in pediatric patients. A guidance document on pediatric pharmacokinetic studies is available [www.fda.gov/cder/guidance/1852fnl.pdf].

In addition, during the "acute phase" of Study II, weekly blood samples will be collected for analysis of lithium in serum. In the "subset group," weekly serial samples will be collected in both serum and whole blood. Distribution of lithium to erythrocytes (the "lithium ratio") should be presented also as a ratio of lithium concentrations in whole blood to serum .

- Pediatric Efficacy and Safety (Study II)

A scale specific to mania and sensitive to the effects of drug treatment of mania in children and adolescents (e.g. Young Mania Rating Scale (Y-MRS)) will be used. If another scale is chosen, choice of the primary assessment instrument and outcome will be justified in the protocol. Specifically, other scales and outcomes used in adult studies need to be validated in the pediatric population.

A primary outcome (or outcomes) must be identified for the controlled efficacy trial. Ordinarily, change from baseline to endpoint on the selected rating scale will be appropriate. Justification of primary endpoint selection will be of particular concern if the definitive effectiveness trial fails to distinguish lithium from placebo.

Secondary outcome assessments should include, but not necessarily be limited to, ADHD symptomatology, aggressive behavior, cognitive and neurologic function, substance abuse, clinical global improvement, and quality of life (including family, school, and peer relationships).

The selection of measures for irritability, aggression/rage, and cognitive function will be justified in the protocol.

Safety assessments as outlined in Study III will also be performed.

- Pediatric Safety (Study III)

Safety assessments must be collected at baseline and protocol specified time periods during follow-up; i.e. vital signs (pulse rate and blood pressure), weight, height by stadiometer, Tanner staging, clinical laboratory measurements (serum lithium levels, chemistry, hematology, urinalysis, drug screens, thyroid function, and renal function), and electrocardiograms. Electro-encephalograms (EEGs) will be performed at baseline and at a protocol specified time period in a random subset of patients. In addition, an EEG will be obtained for any significant deterioration in neurological or cognitive status. All EEGs will be correlated with serum lithium levels. Protocols will provide for timely access to neurologic consultation. Monitoring for adverse events (including toxicities such as dehydration, tremor, ataxia, goiter, and renal dysfunction) and adverse outcomes, (including suicide attempts, relapse, or hospitalization) must also be performed. A serum and whole blood lithium level will be measured if an adverse event occurs.

- Pediatric Long-term Safety Study (Study III)

Safety data must be collected in the controlled efficacy trial. Additionally, longer-term safety data will be collected from open studies (e.g. extension from the controlled study or a separate long-term safety and efficacy trial.) If an adequately designed trial fails to detect a drug effect, you must still collect long-term safety data at doses representative of current use.

Age Group in which Studies will be Performed (all studies)

Pediatric patients age 10-17 years old with acute mania with age, ethnicity, and gender distribution reflecting the epidemiology of bipolar disease must be included in these studies. Younger patients may be included if full *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* (DSM IV) diagnostic criteria for mania are met.

Number of Patients to be Studied:

- Pediatric Pharmacokinetic and Tolerability Study (Study I)

For a traditional pharmacokinetic study, at least 18 pediatric patients (9 males and 9 females) will be enrolled to adequately characterize the pharmacokinetics and tolerability of lithium. If study results are inconclusive or inadequate for characterization of lithium pharmacokinetics and/or tolerability in acutely manic patients, additional patients will be enrolled.

- Pediatric Efficacy and Safety Study (Study II)

The study will have a sufficient number of patients (males and females) to detect a difference between drug and placebo equivalent to the median drug-placebo difference seen in adult trials. A multicenter study will probably be necessary to ensure a sufficient population accurately diagnosed with mania completes the trial.

- Pediatric Long-term Safety Study (Study III)

At least 100 patients exposed to drug for no less than 6 months will be a minimum requirement for long-term safety. You are strongly encouraged to follow these patients for at least a year.

Inclusion/Exclusion Criteria:

The trials will enroll appropriately aged pediatric patients who meet DSM IV diagnostic criteria, as assessed by a semi-structured interview, for mania or mixed episodes in Bipolar I disorder. A well-trained mental health specialist will establish the diagnosis based on two sources of information (e.g. parent, patient, or teacher). Patients will show impairment in one or more settings per DSM IV.

Both hospitalized pediatric patients and pediatric outpatients may be eligible to participate in these trials. Efforts to maximize patient safety will include, but not be limited to, measures such as continuous 24 hour and 7 day per week access to emergency care, inpatient stabilization, suicide precautions and family support. The protocol will specify the washout period for patients currently on psychotropic agents, including stimulants.

Patients with comorbid conditions [attention deficit hyperactivity disorder (ADHD), conduct disorder] may participate in these trials. In addition, patients with a history of substance abuse may participate if they agree to detoxify prior to the trial and have a negative drug screen upon entry. Patients with mental retardation, pervasive developmental disorder, substance induced mania, neurologic disease, substance dependence and serious homicidal/suicidal ideation will be excluded from the trial. Definitions for these conditions will be specified in the protocol. Patients with a history of lithium

Since lithium is considered to be teratogenic (Category D- positive evidence of human fetal risk but benefits may be acceptable), a hormonally based pregnancy prevention plan in female patients of childbearing potential must be implemented to include a pregnancy test at baseline and the end of the trial. The protocol must specify a method for ensuring that trial participants who inadvertently become pregnant receive appropriate antenatal care and counseling. If a trial participant should become pregnant during the study, her offspring will be evaluated for the presence of congenital anomalies, with examination to include echocardiography.

You are encouraged to perform long-term follow up (at 1 year and 18 months) to assess lithium's effect on linear growth and development, as well as adverse events outlined above.

Additional adverse events that occur from the time of initiating lithium administration until the end of trial will be systematically collected and reported. Any adverse event that occurs during treatment will be captured and submitted as part of the study report, as will need for any medical intervention. The circumstances of any deaths, discontinuations, and serious adverse events will be adequately documented and transmitted within the study report. Patients with ongoing adverse events at the trial's conclusion must be followed until these events have resolved.

Statistical Information

The following information will be provided from the Pediatric Pharmacokinetic studies (Studies I and II)

- Descriptive analysis of lithium pharmacokinetic parameters.
- Comparison of pediatric and adult historical lithium pharmacokinetic parameters
- Comparison of lithium pharmacokinetic parameters obtained during steady state and after the first dose (exploring dose- and time-dependency in pharmacokinetics)
- Pharmacokinetic and pharmacodynamic relationships (exploring dose-response relationships) and influence of intrinsic factors (patient characteristics such as age, gender, height, and weight) on lithium clearance
- Distribution of lithium in erythrocytes (exploring lithium distribution characteristics) if evaluated

Pediatric Efficacy and Safety Study (Study II)

- The trial must have a detailed statistical plan. The trial will be designed with at least 85% statistical power to detect a reasonable treatment effect (probably best based on typical efforts in adults) at conventional levels (alpha=0.05, 2 tailed) of statistical significance.

Pediatric Safety Study (Study III)

- Descriptive analysis of the safety data.

GENERAL REQUIREMENTS AND COMMENTS

Drug information:

- Descriptive analysis of the safety data. Existing age appropriate formulations will be used in the studies described above.
- The dosage form used will be justified and specified in the protocols.
- Studies II and III will use the dosing regimen determined in study I.

Drug Specific Safety Concerns:
Potential effects on cognition, growth, thyroid, and renal functions are of particular importance in pediatric patients. Lithium is considered to be teratogenic (Category D- positive evidence of human fetal risk but benefits may be acceptable).

Labeling that may result from the Studies:
Appropriate sections of the label may be changed to incorporate the findings of the pediatric efficacy, safety, and pharmacokinetic 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 are required.

Pharmacokinetic study reports will include analytical method and assay validation, individual drug concentration-time data, and individual pharmacokinetic parameters (and pharmacodynamic 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.

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"** 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"** 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 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, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, by phone at 301-594-2850 or via e-mail at batesd@cder.fda.gov.

Sincerely,

{See appended electronic signature page}

Rachel E. Behrman, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research