DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-427

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta (duloxetine hydrochloride) Delayed-Release 20 mg, 30 mg, and 60 mg Capsules.

We acknowledge receipt of your Proposed Pediatric Study Request dated October 7, 2005, submitted to the duloxetine hydrochloride IND application (38,838).

To obtain needed pediatric information on duloxetine, 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 with Major Depressive Disorder (MDD) described below.

PEDIATRIC MDD

General Advice for Developing a Drug for Pediatric Major Depressive Disorder (MDD)

Under current regulations [21 CFR 201.57(f)(9)(iv) in the 2006 CFR], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that depression was essentially the same disease in adults and children. Under FDAMA (1997), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. At the present time, however, there are insufficient data to support reliance on studies in adults with major depressive disorder to support an indication in pediatrics. Our concern about the extrapolability of adults to pediatric major depressive disorder patients is more than theoretical. While we acknowledge that fluoxetine has been shown to be effective in treating MDD in pediatric patients, other antidepressant drugs have not been reliably demonstrated to be of benefit in treating pediatric MDD. Negative results have been observed not only for the older antidepressants, i.e., tricylic antidepressants, but also for the current generation of antidepressants, with the exception of fluoxetine. Although we recognize that there are many possible explanations for these negative studies, they, nevertheless, lead to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. Consequently, adequate evaluation of the effect of an antidepressant in pediatric major depressive disorder, even for

any antidepressant already approved in adult major depressive disorder, will require two independent, adequate and well controlled clinical trials in pediatric patients, in addition to pharmacokinetic and safety information in the relevant pediatric age groups. For pediatric major depressive disorder, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17).

Specific Study Requirements for Development Program in Pediatric Major Depressive Disorder

Types of Studies

Pediatric Efficacy and Safety Study

Pediatric Pharmacokinetic Study

Pediatric Safety Study

Nonclinical Toxicology

Objective/Rationale

The overall goal of the development program should be to establish the safety and efficacy of the study drug in the treatment of pediatric major depressive disorder, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Efficacy and Safety Studies

- You must conduct two randomized, double-blind, parallel group, placebo-controlled acute treatment trials, with a duration of 6 to 8 weeks. Both trials must include a third fluoxetine arm, because this is the only antidepressant that has been reliably shown to have a benefit in pediatric depression. The fluoxetine arm will provide evidence of assay sensitivity. The trials should allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or those who worsen. At least 50% of patients assigned to active drug must complete to the nominal endpoints of these trials in order for them to be considered completed trials and, therefore, responsive to this request. Complete information should be collected and provided on the reasons for patients leaving the trial. The trials should be designed in a way that fully evaluates the drug in children. Therefore, we strongly recommend that both of the trials have a fixed dose response design, including doses that fully explore the tolerated dose range in this population. In any case, at least one of these two studies must have a fixed dose response design. In addition, we strongly recommend that you conduct a randomized withdrawal trial in which responders to acute treatment, either in one of the acute controlled studies or from open experience, are randomized to study drug or placebo, with follow-up observation for relapse. Patients must be in a responder status for at least 3 months before randomization.

Pediatric Pharmacokinetic Study

- You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to preliminary efficacy trials or to other safety trials. You must perform preliminary tolerability studies (in which kinetic data can be obtained) to fully explore the range of tolerated doses, before conducting the definitive pharmacokinetic study and before conducting the definitive efficacy and safety studies. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

- Safety data must be collected in the controlled efficacy trials. In addition, longer-term safety data, with a minimum duration of 6 months exposure to the drug, must be collected. The longer-term safety data could come from open studies, e.g., the open run-in phase for the randomized withdrawal study and from a longer-term open extension phase of the acute efficacy trials. Adequate longer-term safety data from studies in any indication would be sufficient to meet this requirement. The long-term safety data must be at or above the dose or doses identified as effective in an adequately designed trial, as described above. Even if the controlled trials program fails to detect a drug effect, you must still collect long-term safety data, at doses at least as high as the doses currently used in treating patients off-label with this drug.

Nonclinical Toxicology Study

- In order to support later phase clinical studies in pediatric patients and provide additional safety information for labeling, you must conduct juvenile animal toxicity studies. These studies should utilize animals of an age range and stage(s) of development that are comparable to the intended human population, and the animals should be exposed to the drug for a period that will cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, these studies should evaluate the effects of your drug on growth, reproductive development, and neurological and neurobehavioral development. Reproductive effects need to be evaluated following cessation of treatment; there should be a washout period of appropriate duration (depending on the half-life) between cessation of treatment and evaluation. In assessing neurobehavioral development, the effects should be evaluated during treatment and after an appropriate washout period following the cessation of treatment (to evaluate potential long-term effects). To avoid the confounding effect of repeated neurobehavioral testing, separate groups of animals should be used at the two assessment times. However, to avoid unnecessary use of animals, the same group of animals may be used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests should assess sensory function, motor function, and learning and memory. The neuropathological evaluation should include examination of all major brain regions and cellular elements, with particular attention to alterations indicative of developmental insult.

  Protocols for juvenile toxicity studies should be submitted to the Division for comment prior to initiation.

<u>Age Group in Which Study(ies) will be Performed –All Studies</u>

Both children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) should be approximately evenly distributed over the age range in the study (at least 40% in younger stratum), and the numbers of male and female patients should be approximately equal within these samples as well.

Number of Patients to be Studied

Pediatric Efficacy and Safety Studies

- The studies must have sufficient numbers of patients to provide 80% statistical power to show a meaningful difference between drug and placebo. While it is difficult to specify the sample size needed to accomplish this, it should be noted that positive trials in pediatric major depressive disorder have generally utilized samples of about 100 patients per treatment arm. It will probably be necessary to conduct multicentered studies to ensure a sufficient population accurately diagnosed with pediatric MDD.

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug in the above age groups. The full spectrum of age strata in the 7 to 17 continuum must be represented (e.g., 7-9, 10-12, 13-14, 15-17) and must have at least 4 completers per strata. Data from this study must be submitted prior to the start of the safety and efficacy study.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of the study drug at clinically relevant doses for a duration reflecting actual use. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

Entry Criteria

The protocols must include a valid and reliable diagnostic method for recruiting and enrolling children and adolescents with MDD. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g., child psychiatrist or other clinician adequately trained to conduct such interviews) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Efficacy and Safety Studies

- A scale specific to pediatric MDD and sensitive to the effects of drug treatment of MDD in the target population should be used, e.g., the Children's Depression Rating Scale-Revised. It may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI). It is essential to identify a primary outcome (or outcomes if more than one is considered important) for the controlled efficacy trials; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.

Pediatric Pharmacokinetic Study

- Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected should provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max} , T_{max}, and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

Pediatric Safety Study

- Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., vital signs (pulse rate and blood pressure), weight, height, as measured by stadiometer, clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Given recent concerns about possible induction of suicidality with antidepressant drugs, more specific ascertainment for emerging suicidality should be added to these trials. Assessment for the effect of the study drug on the growth and development of pediatric patients is critical, and you must incorporate specific measures to assess changes in height and weight (e.g., stadiometer height measurement).

Statistical Information

Pediatric Efficacy and Safety Studies

- These trials must have detailed statistical plans. The trials should be designed with at least 80% statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults) at conventional levels (alpha=0.05, 2-tailed) of statistical significance. Previous antidepressant trials that have succeeded in pediatric depression have generally had sample sizes of about 100 patients per treatment arm. The statistical analysis plan must be submitted for comment prior to initiating efficacy and safety studies.

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

GENERAL REQUIREMENTS AND COMMENTS

Drug Information

- Use age appropriate formulations in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial

marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug Concerns

- No specific concerns related to administration to pediatric patients were identified while studying duloxetine in adults.

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. 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.

Timeframe for Submitting Reports of the Studies

- Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please 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 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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. 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 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, 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.

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/Summaryreview.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/.

If you have any questions, contact Dr. Renmeet Gujral, Regulatory Project Manager, at (301) 796-1080.

Sincerely yours,

{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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