DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT

NDA 21-427

Eli Lilly & Company
Attention: Bryan Boggs, Pharm.D
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Boggs:

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.

Reference is also made to the Agency's original pediatric Written Request letter dated June 23, 2006, your correspondence to the Agency dated October 17, 2008 requesting changes to the Written Request, a meeting between Lilly and the Agency on November 7, 2006 discussing these changes, and the Agency's amended Written Request letter dated September 22, 2009.

We acknowledge receipt of your e-mail communication dated September 25, 2009, conveying your concerns about the inclusion of new timing requirements contained in the Best Pharmaceuticals for Children Act (BPCA) of 2007, and that the Cymbalta Written Request should be governed by the timeframe in the BPCA of 2002.

We concur with your assessment, and we are therefore amending the Written Request to remove the language below from the "Timeframe for Submitting Reports of the Studies" sections of the letter.

> [deletion of the following language]
> Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

All other terms stated in our Written Request issued on June 23, 2006, and amended on September 22, 2009 remain the same.

For your convenience, the full text of the June 23, 2006 Written Request, as amended by our September 22, 2009 letter and revised to reflect the above changes, is 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., tricyclic 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

<u>Types of Studies</u>

Pediatric Efficacy and Safety Study

Pediatric Pharmacokinetic Study

Pediatric Safety Study

Nonclinical Toxicology

<u>Objective/Rationale</u>

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.

Age Group in Which Study(ies) will be Performed –All Studies

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 appropriate dose range, tolerability, and pharmacokinetics of the study drug and its major active metabolite(s) in the relevant age group must be studied. 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 should have at least 4 completers per stratum. A study should be designed with

sufficient N to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution. If statistical power is not attained in this preliminary tolerability study, an additional intensive sampling pharmacokinetic study or population pharmacokinetic study (i.e., during the definitive efficacy and safety trials) can be conducted. Final power will be estimated from the combined N of the tolerability and pharmacokinetic studies. Data from the tolerability studies should be accumulated prior to the start of the definitive safety and efficacy trials.

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.

- Statistical Information (including Power of Studies and Statistical Assessments): Efficacy studies must be sufficiently powered to assess the efficacy of both the lower dose arm (duloxetine 30 mg qd) and the active control arm (fluoxetine) to determine effectiveness compared to placebo, in addition to assessing the efficacy of other doses of duloxetine (e.g. duloxetine 60 mg dose arm).

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 Specific Safety Concerns

- Post-market reporting suggests that duloxetine may contribute to hepatic injury in adults; therefore, this issue needs to be assessed in the pediatric safety studies. Liver function tests should be monitored in all short term and long term safety pediatric studies, comparing several time points to baseline values.

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 on or before March 31, 2013.

Reports of the studies that meet the terms of the Written Request dated June 23, 2006 and amended by our September 22, 2009 letter and this letter must be submitted to the Agency on or before March 31, 2013, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are 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. In addition, send a copy of the cover letter of your submission, via fax (301-827-5911) 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, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that duloxetine is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. 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).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call LCDR Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager, at 301-796-1080.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
[redacted]			(b) (4)
NDA-21427	GI-1	ELI LILLY AND CO	CYMBALTA(DULOXETINE HCL)20,30,(b) (4)6OMG

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/s/

ROBERT TEMPLE
11/02/2009