DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021368
(b) (4)
IND 116994

WRITTEN REQUEST – AMENDMENT 3

Eli Lilly and Company
Attention: Carlos O. Garner, Ph.D.
Senior Director, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Garner:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adcirca (tadalafil) tablets and Cialis (tadalafil) tablets.

(b) (4)
the pediatric Written Request (WR) for tadalafil which was originally issued on November 16, 2006 and subsequently amended on April 12, 2010 (Amendment 1) and September 17, 2015 (Amendment 2). (b) (4)
the tadalafil WR be (b) (4) asking for submission of appropriate studies in patients with (b) (4) Duchenne muscular dystrophy (DMD) (b) (4)

I also refer to the following:

(b) (4)

:

- There continues to be a strong public health interest in obtaining additional information about the use of tadalafil in (b) (4) DMD populations

(b) (4)

- The current WR includes work to be conducted in children with DMD. These studies are important to inform the use of tadalafil and should remain a part of the tadalafil WR

(b) (4)

(b) (4) Reports of the studies that meet the terms of the Written Request, as amended by this letter and by previous amendment dated April 12, 2010, must be submitted to the Agency on or before August 19, 2019, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. The Written Request now stands as:

DUCHENNE MUSCULAR DYSTROPHY

BACKGROUND

Tadalafil (Cialis, Adcirca) is indicated for the treatment of adult patients with erectile dysfunction, for the treatment of pulmonary arterial hypertension, and for the treatment of benign prostatic hyperplasia. The Written Request will include one phase 3 study to investigate the potential use of tadalafil in the treatment of Duchenne muscular dystrophy (DMD). Tadalafil is a selective, reversible inhibitor of cGMP-specific PDE5 that might increase perfusion of muscle tissue and thereby reduce ischemic muscle injury in the disease.

DMD is a progressive, X-linked recessive muscle disorder that leads to loss of ambulation, cardiac and respiratory failure, and death typically by age 30. The disease affects approximately 1 in 3600-6000 male births. Current treatments are limited to corticosteroids and supportive care.

Studies in pediatric patients less than 7 years of age with DMD, including neonates, are not required as part of this Written Request because tadalafil is intended to treat a pediatric patient population that is ambulatory and beginning to develop weakness affecting quality of life. Boys younger than 7 years may have developmental gait improvement, whereas after age 7 the disease progression begins to overcome

developmental gains. Patients above age 14 are not being studied because they are likely to have lost ambulation. Efficacy for pediatric patients with DMD cannot be extrapolated from adults because the efficacy of tadalafil has not been established in adults with DMD. Tadalafil is not approved for DMD in any pediatric age group. Therefore, the studies included in the Written Request are intended to establish efficacy for use of tadalafil in DMD.

To obtain needed pediatric information on tadalafil, 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), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- ***Nonclinical study*:**

A juvenile animal toxicology study in rat must be conducted to support the safety of tadalafil in pediatric DMD patients. The dosing period must encompass an age range and stage(s) of development comparable to the intended pediatric patient population (i.e., postnatal days 7 through 60).

- ***Clinical study:***

A Phase 3, multicenter, randomized, double blind, placebo-controlled, parallel, 3-arm study to test the hypothesis that once daily tadalafil administered orally for 48 weeks lessens the decline in ambulatory ability as measured by the 6-Minute Walk Distance (6MWD) compared to placebo in ambulatory males with DMD, age 7 to 14 years (the approximate age of loss of ambulation), who are already receiving treatment with corticosteroids. Tadalafil pharmacokinetics (PK) and relationships between tadalafil exposure and efficacy and safety will be characterized using a population PK (PPK) approach. Patients will be randomized to one of two doses of tadalafil or placebo in a 1:1:1 ratio).

Patients will continue to be followed in a 48-week extension safety study that captures known and/or unexpected adverse reactions. This extension study does not need to be completed to fulfill the Written Request, but the study will need to be initiated and an interim clinical study report with datasets containing at least 6 months of evaluable safety data must be submitted to the Agency to fulfill the Written Request. No fewer than 160 subjects are to be enrolled for evaluation of safety.

- *Objective of the study:*

The objective of the phase 3 efficacy trial is to determine if once daily tadalafil administered orally for 48 weeks lessens the decline in ambulatory ability in boys with DMD age 7 to 14 years.

- *Patients to be Studied:*

    - *Age group in which study will be performed:* Ages 7 to 14 years
    - *Number of patients to be studied:* At least 300 male patients age 7 to 14 years will be randomized.

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation why they were unsuccessful.

- *Study endpoints:*

    - *Pharmacokinetic/Pharmacodynamic Endpoints:*
        - The pharmacokinetic endpoints in the population pharmacokinetic analysis must include volume of distribution and clearance. Sparse pharmacokinetic samples must be collected to explore the relationships between tadalafil exposure and efficacy and safety endpoints.

- *Efficacy Endpoints:*
    - The primary efficacy endpoint must be the 6MWD and must be assessed by the comparison of the change in the 6MWD after 48 weeks in tadalafil and placebo patients.
    - Important secondary endpoints must include North Star Ambulatory Assessment, time to rise from floor from supine position, 10 meter walk/run time, and 4-stair climb and descend time.

- *Safety Endpoints:*

  Safety must be assessed through periodic measures of vital signs (heart rate and blood pressure), cardiac function (ECGs, echocardiography) and laboratory measures (including serum creatinine). Other safety parameters that must be measured are also described under known drug safety concerns and monitoring. Safety must be assessed for double-blind and open-label periods separately. The safety assessment for the open-label period can be descriptive.
    - A Data Monitoring Committee (DMC) must be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM12657 8.pdf.

- *Known drug safety concerns and monitoring:*

  The following known drug specific safety concerns must be actively monitored, assessed with the appropriate methodology when indicated (e.g., ECG, medical imaging, ophthalmological exam, etc.), and reported: angina, MI, stroke, hypotension, hypertension, syncope, tachycardia, priapism, vision loss, hearing loss, non-arteritic anterior ischemic optic neuropathy, Stevens-Johnson syndrome, exfoliative dermatitis. If patients develop any of these adverse events, they must be monitored until symptom resolution or until the condition stabilizes. The following adverse events must be captured when spontaneously reported: headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, limb pain.

- *Extraordinary results:*

  In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

    - *Dosage form:* The tadalafil formulations for use in the clinical study are the commercial 2.5-mg, 5-mg, 10-mg, and 20-mg Cialis tablets.

  - *Route of administration:* oral.

  - *Regimen:* Patients who meet all eligibility criteria must be randomized to receive one of 2 target doses of tadalafil (0.3 mg/kg or 0.6 mg/kg) or matching placebo once daily for 48 weeks. These once-daily doses are predicted to achieve steady-state exposures consistent with those that produced pharmacological effects on skeletal muscle hemodynamics in boys with DMD after a single dose.

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  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 prepared by a licensed pharmacist, in a licensed pharmacy, from commercially

available ingredients. Under these circumstances, 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

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

- *Statistical information, including power of study(ies) and statistical assessments*:

A single interim analysis for futility will be conducted when approximately 50% of patients have completed the 48-week blinded treatment phase. The study must be powered to detect a between-group difference in mean change in 6MWD distance of 30 meters. Assuming a common standard deviation of 60 meters, a sample size of 102 patients for each of the three treatment groups is expected to provide approximately 90% power to detect a placebo-adjusted difference of 30 meters in change in 6MWD. This calculation is based on testing each dose level versus placebo using a two-sided t-test at the 0.025 significance level without adjustment for dropouts (all patients with baseline and post-baseline measures are to be included in the primary analyses).

With respect to the primary efficacy analysis, the protocol will describe the estimand of primary interest. If the estimand of interest is the treatment effect in all patients randomized regardless of adherence, you should include provisions to limit missing data through the study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation, following the recommendation from the National Research Council of the National Academies of Sciences (NAS) report on missing data in clinical trials. If you believe the treatment effect in all patients randomized regardless of adherence is not the most clinically important estimand, the protocol should specify which estimand is of most clinical importance and why. Statistical methods to quantify this estimand should be specified in the protocol.

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 (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 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:

- In accordance with section 505A(e)(2), 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 indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that tadalafil 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:

  - the type of response to the Written Request (i.e., complete or partial response);
  - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
  - the action taken (i.e., approval, complete response); or
  - the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

- 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 Yvette Choy, Regulatory Project Manager, at 301-796-2899.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
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/

ELLIS F UNGER
08/03/2017