



NDA 022332/S-006

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Katherine E. Broderick, PharmD
Global Regulatory Affairs – US, Advisor
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Broderick:

Please refer to your Supplemental New Drug Application (sNDA) dated and received April 1, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adcirca (tadalafil) 20 mg Tablets.

We also refer to our March 11, 2014 letter, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for phosphodiesterase type 5 inhibitors (PDE5 inhibitors). This information pertains to the risk of non-arteritic anterior ischemic neuropathy (NAION).

This supplemental new drug application provides for revisions to the labeling for Adcirca, consistent with our March 11, 2014 letter. The revisions are as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text):

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was added:

Warnings and Precautions, Visual Loss (5.5) 04/2014

2. Under **WARNINGS AND PRECAUTIONS**, the following text was added/deleted:

5.5 Visual Loss~~Effects on the Eye~~

Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision, that has been reported ~~rarely~~ postmarketing in temporal association with the use of all PDE5 inhibitors. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥ 50 in the

general population. An observational study evaluated whether recent episodic use of (b) (4) PDE5 inhibitors, as a class, typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within 1 to 4 days of PDE5 inhibitor use.

It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors (b) (4)

[REDACTED]

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

3. Under **ADVERSE REACTIONS**, the following text was added/deleted:

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension [*see Warnings and Precautions (5.1)*]
- Visual Loss~~Effects on the Eye~~ [*see Warnings and Precautions (5.5) and Patient Counseling Information (17)*]
- Hearing loss [*see Warnings and Precautions (5.6)*]
- Priapism [*see Warnings and Precautions (5.8)*]

4. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following text was deleted:

~~Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors [*see Warnings and Precautions (5.5) and Patient Counseling Information (17)*].~~

5. There are a few editorial revisions noted: the deletion of the cross reference to 6.2 from the 6th bullet in Highlights/Warnings and Precautions; the Table of Contents was updated to reflect the change in section 5.5.

The sponsor made the following changes to the **Patient Package Insert**:

6. Under the **What are the possible side effects of ADCIRCA?** section, the following text was deleted:

- Decreased eyesight or loss of vision in one or both eyes (NAION). If you notice a sudden decrease or loss of vision in one or both eyes, contact a healthcare provider right away. ~~It is not possible to determine whether these events are related to oral medicines for the treatment of erectile dysfunction, including tadalafil, or to other medical problems, or to a combination of these.~~
- Sudden decrease or loss of hearing, sometimes with ringing in the ears and dizziness. If you notice a sudden decrease or loss of hearing, contact a healthcare provider right away. ~~It is not possible to determine whether these events are related to oral medicines for the treatment of erectile dysfunction, including tadalafil, or to other medical problems, or to a combination of these.~~
- In men, an erection that lasts more than 4 hours (with or without pain). Talk to your healthcare provider or go to the emergency department right away. An erection that lasts more than 4 hours must be treated as soon as possible or you can have lasting damage to your penis, including the inability to have erections.

There are no other changes from the last approved package insert.

APPROVAL & LABELING

We have completed our review of this supplemental application and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
04/29/2014