

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-368

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-368

Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

Please refer to your new drug application dated June 28, 2001, received June 29, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cialis® (tadalafil), tablets 5mg, 10mg and 20mg.

We acknowledge receipt of your submissions dated June 28, July 24, August 27, September 10, 17, 18, and 25, October 1, 22, 25, and 30, November 5, and December 6, 2001; January 14 and 23, February 1, 6, 26, and 28, March 4, 6, 12, 18, 20, 22, and 25, April 1, 4, 5, and 16, May 10 (2), 14, 16, 24, and 30, June 6, 13, and 28, August 6, 8, 22, and 26, September 5, 12, 24, and 30, November 15 and 27, 2002, February 13, April 16 and 24, May 16, 27, and 30, June 5, 17, 24, and 26, July 15 and 22, August 7, 11, 19, and 29, September 11, October 9, 14, 15, 20 (2), and 24 (2), and November 5, 11, 12, 17, 19, and 20, 2003.

The May 27, 2003 submission constituted a complete response to our April 29, 2002 action letter.

This new drug application provides for the use of Cialis® (tadalafil) tablets for the treatment of erectile dysfunction.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-368." Approval of this submission by FDA is not required before the labeling is used.

We remind you of the postmarketing study commitment you made in a letter dated November 19, 2003. The commitment is listed below:

1. To conduct a randomized, placebo-controlled study investigating the effects of Cialis® (tadalafil) tablets on color vision and retinal physiology (electroretinography) following multiple daily doses. The timeline is as follows:

Protocol Submission	within 3 months of the date of this letter
Study Initiation	within 10 months of the date of this letter
Final Report Submission	within 18 months of the date of this letter

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Physician Insert
Patient Package Insert

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
21-368

APPROVABLE LETTER



NDA 21-368

Lilly ICOS LLC
Lilly Research Laboratories
Attention: Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated June 28, 2001, received June 29, 2001, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cialis (tadalafil).

We also acknowledge receipt of your submissions dated July 24, August 27, September 10, 17, 18, and 25, October 1, 22, 25, and 30, November 5, and December 6, 2001, January 14, 23, February 1, 6, 26, and 28, March 4, 6, 12, 18, 20, 22, and 25, April 1, 4, 5, and 16, 2002.

We have completed our review and find your application, as amended, for marketing of Cialis 5mg, 10mg, and 20mg tablets is approvable. Your efficacy data demonstrate that 10mg would be an appropriate starting dose for most men with erectile dysfunction. The FDA believes that a range of dosage strengths are needed to promote effective treatment of the spectrum of erectile dysfunction and to promote safety through use of the lowest effective dose. Before the application may be approved, it will be necessary for you to address the following deficiencies:

Clinical:

1. We agree that use of Cialis should be contraindicated for patients on continuous or intermittent nitrate therapy. However, it is expected that men with cardiovascular disease will use Cialis. Some of these men will experience cardiovascular events and be given nitrates in emergency situations. You must provide information to label the effects of blood pressure with nitroglycerin and Cialis 20mg for a period of time after Cialis dosing until no blood pressure interaction is seen.

The following information is needed to address this deficiency:

Conduct studies on patients treated with daily doses of Cialis (20mg or higher) at steady state with administration of nitrates at various times following the last dose of Cialis to determine at what point after Cialis dosing there is no apparent blood pressure interaction. This study should include elderly subjects (who may have higher exposure and a longer half-life than younger subjects). We recommend that you submit your proposed protocol so that the Division of Cardio-Renal Drug Products (DCRDP) can assess the acceptability of the protocol to fulfill this requirement.

Propose a plan for patient and physician education regarding nitrate contraindication and nitrate interaction.

2. Alcohol is expected to be used in social situations where Cialis may be taken. Your application provided data on alcohol interaction; however, results from the 10mg study differ from the 20mg Cialis study with respect to clinically significant changes in blood pressure.

The following information is needed to address this deficiency:

Conduct another study of alcohol interaction with the 20mg dose of Cialis and alcohol at a dose of 0.7 g/kg. Monitor blood alcohol and Cialis levels during the study.

3. QT prolongation may be a signal for life-threatening cardiac adverse events. Cialis has known drug interactions that can significantly elevate drug exposure. Therefore, it is important to rule out QT effects due to Cialis. Although your application contains QT studies, this information is insufficient to make such a conclusion. More clinical information is needed to ensure there is no QT effect.

The following information is needed to address this deficiency:

Conduct a study that includes a sufficient number of patients to provide reliable results on doses of 80mg or higher of Cialis. There must be a placebo control arm. An additional positive control arm is desirable. Include an assessment of the potential for the methylcatechol glucuronide metabolite to prolong the QT interval. We recommend that you submit your proposed protocol so that DCRDP can assess the acceptability of the protocol to fulfill this requirement.

4. Our clinical pharmacology review found that "myalgia" and "back pain" tend to occur at the time of the peak concentration of the methylcatechol glucuronide metabolite, which is not specific for PDE5 receptors. These events also occur more commonly with higher exposures of Cialis, as seen in the elderly. Provide information that these adverse events do not reflect medically significant underlying pathology.

The following information is needed to address this deficiency:

Analyze reports of "myalgia" and "back pain" for severity, medical intervention required, hospitalization, discontinuation from study, etc. Patients who develop "myalgia" or "back pain" in on-going and new studies, especially studies utilizing higher doses of Cialis, must be analyzed in this respect and must undergo further work up to rule out medically significant disease process. Include an assessment for vasculitis and for any direct effect of Cialis or the methylcatechol glucuronide metabolite on the kidney. We recommend that you submit the plans for medical work up of these adverse events to the Division of Reproductive and Urologic Drug Products (DRUDP) for concurrence.

Chemistry, Manufacturing, and Controls

5. The Office of Compliance recommended that DRUDP withhold approval of Cialis because of deficiencies in current good manufacturing practices (cGMP).

The following information is needed to address this deficiency:

Demonstrate a satisfactory resolution to the deficiencies in current good manufacturing practices noted in the drug product manufacturing site inspection by attaining an acceptable inspection report.

In addition, we recommend that you contact DRUDP to obtain agreement on how you plan to address the following deficiencies:

1. Provide the following information relevant to the cardiovascular safety of Cialis:
 - a) A full characterization and analysis of the medically significant cardiovascular adverse events reported in the NDA (including syncope, angina pectoris, chest pain, unstable angina, myocardial infarction, heart failure, cerebrovascular accident, and cardiac arrest) that address any potential relationship to Cialis. This should include an evaluation from time of last dose to time of event and any plausible mechanism for a drug-related effect.
 - b) Address insufficient diary, medicine card, or other primary data in some patients who experienced serious adverse events including death (including 602-6077, 007-3072, 105-2107, 043-4065, 102-2036, 220-3256, 817-8600, 408-1084, 004-4087, and others).
 - c) Submit the results from Study LVBZ that investigates the effect of Cialis on coronary blood flow.
 - d) Submit the results from Study LVCP that investigates the effect of Cialis on exercise tolerance in men with stable coronary artery disease.
2. Provide information to support labeling regarding interactions of 20mg Cialis with the following: ketoconazole 400mg, ritonavir, doxazosin, or terazosin (in doses used for symptoms of benign prostatic hypertrophy), other relevant anti-hypertensive medications, warfarin, and aspirin.
3. Provide data for labeling on quantitative effects of Cialis on color vision and retinal physiology (as measured by ERG testing). Testing after repeat dosing of Cialis 20mg must be performed.
4. All but 47 of the 119 diabetic patients who received the 20mg dose in pivotal phase 3 trials were pre-screened to exclude those with orthostatic hypotension at baseline. Provide information on those diabetics excluded from the trial and address safety of diabetic patients anticipated in the postmarketing setting (i.e., without screening for orthostatic hypotension).
5. Less than 1% of the clinical trial population (all performed outside US) was of African origin and only 2 to 3 % of Spanish origin. Provide information to show that results from these trials can be applied to the U.S. population.

Comments on labeling are deferred until the above deficiencies are addressed.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - b. Present tabulations of the new safety data combined with the original NDA data.
 - c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this Division, the Division of Reproductive and Urologic Drug Products to discuss what steps need to be taken before the application may be approved.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D.

Director

Office of Drug Evaluation III

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/

Florence Houn
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