

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-332

OTHER REVIEW(S)

22-332 ADCIRCA® (tadalafil) 20 mg Tablets

Project Manager Overview

NDA 22-332 (pulmonary arterial hypertension)
ADCIRCA® (tadalafil) 20 mg Tablets
Pharmacologic Class: PDE-5 Inhibitor
Chemical Classification: Type 6 NDA (new indication)
Orphan Designation

Background

On November 21, 2003, the Division of Reproductive and Urologic Products approved CIALIS (tadalafil) 2.5, 5, 10, and 20 mg tablets for treatment of erectile dysfunction (NDA 21-368).

On July 24, 2008, FDA received Eli Lilly and Company's NDA 22-332 for ADCIRCA (tadalafil) 20 mg oral tablets for the treatment of pulmonary arterial hypertension to improve exercise capacity. The sponsor's proposed dosage is 40 mg (two 20 mg tablets) taken once daily. All studies in support of this application were conducted under IND 71,871 or are cross-referenced to the CIALIS drug development program.

The sponsor conducted study LVGY, a 16-week, parallel, placebo-controlled study using 6MWD as the primary endpoint.

The Division reviewed this NDA under the Good Review Management Principles and Practices—the NDA was assigned a Standard review (10-month clock).

NDA Reviews and Memos

Division Director's Memo

Dr. Norman Stockbridge; May 15, 2009

Regulatory Decision: Approval

As stated in his memo, Dr. Stockbridge recommends 40 mg once daily, reducing to 20 mg if necessary, based on individual tolerability (in contrast to the conclusion reached by the clinical pharmacology and pharmacometrics reviewers).

CDTL Memo

Dr. Tom Marciniak; April 20, 2009

Dr. Marciniak recommends starting patients at 40 mg once daily, not 20 mg as suggested in the clinical pharmacology review (see memo for details).

JOINT CLIN/STAT REVIEW

Clinical Review; Dr. Maryann Gordon: March 12, 2009

Statistical Review; Dr. Valeria Freidlin: March 30, 2009

Recommended Action: Approval

Comments included in the review: The sponsor should evaluate higher doses of tadalafil since only the 40 mg dose was shown to be effective in improving exercise capacity; the 20 mg once daily dose was marginally effective and doses lower than 20 mg had effects similar to placebo. There are no obvious dose-limiting serious adverse events. Also, a drug interaction study with ambrisentan is being recommended.

DSI: December 24, 2008 report (Jeremy Feldman) – VAI

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Clinical Pharmacology and Pharmacometrics; March 27, 2009

Dr. Islam Younis

Dr. Keven Krudys

Recommended Action: Approval

Comments included in the review: The starting dose should be 20 mg QD and increased to 40 mg if deemed appropriate. No dose adjustment is needed when given with bosentan. Labeling recommendations have been provided (see section 12.2 of the PI). No PMCs/PMRs are being recommended.

Pharmacology Review; March 6, 2009

Dr. John Koerner

Recommended action: Approval

Comments included in the review: No additional non-clinical studies are being recommended and the sponsor's proposed labeling text is adequate.

Chemistry Review; March 10, 2009

Dr. Donald Klein

Recommended action: Approval

Comments: The proposed carton, container, and labeling is acceptable from a CMC viewpoint. No additional CMC-related studies are being proposed. The sponsor's request for categorical exclusion of an environmental assessment is acceptable. The proposed 36-month expiry dating should be granted.

OSE Review

In a review dated May 20, 2009, the Division for Medication Error Prevention and Analysis found that the proposed trade name ADCIRCA does not appear to be vulnerable to name confusion that could lead to medication errors.

Comments sent to the sponsor on May 15, 2009 regarding the **proposed container label** were as follows:

1. Ensure that the label displays the proprietary name, established name and dosage form in the usual presentation. According to CFR 201.57(2), the usual presentation on the label consists of the proprietary name and the established name immediately followed by the drug's dosage form (i.e. tadalafil tablets). [Also], you are missing the word "tablets" after the established name.
2. Consider mentioning in the label the statement, 'Same active ingredient as Cialis', to ensure that practitioners are aware of the dual proprietary name issue and to avoid medication errors (i.e., concomitant administration) which may occur when a dual proprietary name is introduced to the market.

The OSE reviewer also had other recommendations as follows:

A. Proprietary Name

1. Monitor for concomitant administration of these products and the adverse events associated with the concomitant use of both marketed drug products and provide us with medication error reports regardless of adverse event.
2. Inform healthcare professionals that the same molecular entity will have two different proprietary names and ensure that providers are made aware of the issues that may arise with the introduction of this new name into the market, i.e. patients taking both medications at the same time, awareness of medications to avoid while using, etc.
3. Ensure that patients are aware that the safety concerns associated with Cialis would be the

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same for Adcirca and that Adcirca contains the same active ingredient as Cialis and should not be taken at the same time.

4. Ensure that the container labels and carton labeling include the statement "Same active ingredient as Cialis".

B. Product Strength

We note you have chosen to only develop a 20 mg tablet, although the recommended daily dose is 40 mg. This disparity in strength and dose introduces an unnecessary risk for medication errors as patients could either take 1 tablet twice a day resulting in a sub therapeutic response or only take one tablet once daily, also resulting in a sub therapeutic response. Additionally a prescriber might assume because it is the only dose manufactured, it is the correct dose and prescribe 20 mg instead of 40 mg. Only manufacturing the 20 mg tablet may increase diversion for unintended use with the indication of erectile dysfunction, as 20 mg is the maximum dose intended for erectile dysfunction for Cialis (Tadalafil). By producing the 40 mg tablet, this may decrease the likelihood of using Adcirca for an indication other than the approved indication of pulmonary arterial hypertension and may minimize the potential for dosing errors.

C. Labels and Labeling

1. Ensure that the label displays the proprietary name, established name and dosage form in the usual presentation, i.e. Adcirca (Tadalafil) tablets 20 mg
2. The label should contain the statement, 'Same active ingredient as Cialis', to ensure that practitioners are aware of the dual proprietary name issue and to avoid medication errors (i.e. concomitant administration) which may occur when a dual proprietary name is introduced to the market.

In response to OSE's comments, the **immediate container label** will be updated with the statement 'Same active ingredient as Cialis'. Furthermore, the package insert addresses the concern in the **Warnings and Precautions** section as follows:

5.7 Combination with Other PDE5 Inhibitors

Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- Inform patients that tadalafil is also marketed as CIALIS for erectile dysfunction. Advise patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.

With regard to development of a 40 mg tablet, DCRP agrees that taking two 20 mg tablets is not ideal, however, given that virtually no dose-response relationship was observed on 6MW between 20 mg and 40 mg and given that taking less does not pose any obvious safety concerns, DCRP has elected to approve the 20 mg tablet and not to ask the sponsor to develop a 40 mg tablet at this time.

Action Items: An approval letter will be drafted for Dr. Stockbridge's signature and we will request that the sponsor submit SPL within 14 days of the action.

Reviewed by Daniel Brum, PharmD, MBA, RAC; 5/22/09

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/s/

Dan Brum
5/22/2009 08:43:11 AM
CSO

Internal Consult

****** Pre-decisional Agency Information ******

To: Dan Brum, RPM
Division of Cardiovascular and Renal Products
Office of New Drugs

From: Zarna Patel, Pharm.D., Regulatory Review Officer
Lisa Hubbard, R.Ph., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)
Office of Medical Policy (OMP)

Through: Jialynn Wang, Pharm.D., Group Leader, DDMAC, OMP
Marci Kiester, Pharm.D., Group Leader, DDMAC, OMP

Date: April 6, 2009

Re: NDA # 22-332
Adcirca (tadalafil) Tablets for Oral Administration
Comments on package insert and patient package insert

DDMAC has reviewed the proposed product labeling (PI) and patient package insert (PPI) for Adcirca (tadalafil) Tablets for Oral Administration. The comments below are based on the eCTD NDA submission dated July 24, 2008.

Package Insert

Highlights

DDMAC recommends removing phrases such as _____ from the WARNINGS AND PRECAUTIONS section of the Highlights section of the PI. (Please see section 5.1 below.)

b(4)

In order to prevent minimization of risk within a promotional context, DDMAC recommends presenting the most serious risks first in the USE IN SPECIFIC

5 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Lisa Hubbard
4/6/2009 01:04:06 PM
DDMAC PROFESSIONAL REVIEWER