

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-332

CHEMISTRY REVIEW(S)

NDA 22-332

ADCIRCA™ (tadalafil) Tablet

Eli Lilly and Company

Chemistry Review

Donald N. Klein, Ph.D.

**Branch VII
ONDQA**

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CHEMISTRY NDA REVIEW DATA SHEET

NDA 22-332 ADCIRCA™ (tadalafil) Tablet

1. **CHEM. REVIEW:** # 1.
2. **REVIEW DATE:** March 10, 2009.
3. **REVIEWER:** Donald N. Klein, Ph.D.
4. **PREVIOUS DOCUMENTS:**
 NDA 21-368, Cialis® (tadalafil) Tablet, 20 mg: Approved 11/21/2003 for erectile dysfunction.

5. **SUBMISSION BEING REVIEWED:**

<u>Submissions Reviewed</u>	<u>Document Date</u>
IND 71,871 Pre-NDA Meeting Minutes	26-FEB-2008
Original	24-JUL-2008
CMC Memo to File	02-SEPT-2008
Filing meeting	04-SEPT-2008
Response (<i>e-mail from OND PM</i>)	05-SEPT-2008
74 Day Filing Letter	30-SEPT-2008
(BC) Amendment	13-OCT-2008
Communication with Compliance (<i>e-mail</i>)	04-NOV-2008
Communication with Compliance (<i>e-mail</i>)	06-NOV-2008
Internal NDA review team meeting	15-DEC-2008
CMC Information request (<i>via OND PM</i>)	15-DEC-2008
Response (<i>via OND PM</i>)	15-DEC-2008
Response (<i>via OND PM</i>)	21-DEC-2008
Mid-cycle NDA review team meeting	12-JAN-2009
Draft labeling circulated to review team	17-FEB-2009
Communication with Compliance (<i>e-mail</i>)	26-FEB-2009
Communication with Compliance (<i>e-mail</i>)	27-FEB-2009
(BL) Amendment	02-MAR-2009
CMC Information Request (<i>via OND PM</i>)	06-MAR-2009
Response (<i>via OND PM</i>)	09-MAR-2009

CMP **CHEMISTRY REVIEW** **CMP**

6. **NAME AND ADDRESS OF APPLICANT:**
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
7. **DRUG PRODUCT NAME:**
Proprietary: ADCIRCA™.
Nonproprietary/USAN (2001): Tadalafil.
Code Name/Number for Tadalafil: IC351; LY450190.
8. **LEGAL BASIS FOR SUBMISSION:** Orphan Drug Designation granted on
December 18, 2006.
a. **Chemical Type and Potential:** 6S.
9. **PHARMACOLOGICAL CATEGORY/INDICATION:** Treatment of pulmonary arterial
hypertension (PAH).
10. **DOSAGE FORM:** Immediate release tablet which is orange colored; almond shaped,
film-coated, and debossed with **4467**.
11. **STRENGTH:** 20 mg.
12. **ROUTE OF ADMINISTRATION:** Oral.
13. **DISPENSED:** x RX OTC.
14. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** Yes x No.

15. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

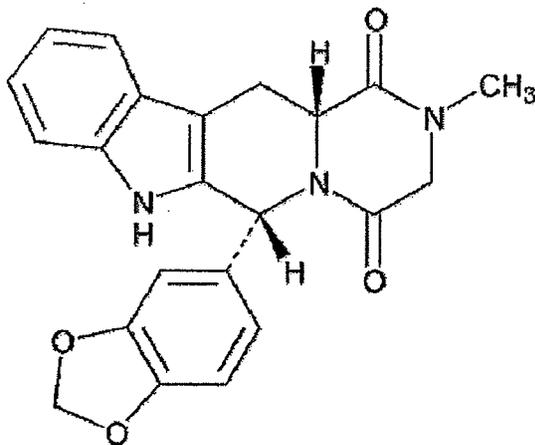
Chemical Name: Pyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6*R*-12a*R*)-.

Molecular Formula: C₂₂H₁₉N₃O₄.

MW: 389.40.

CAS: 171596-29-5.

Chemical Structure:



CHEMISTRY REVIEW

16. RELATED/ SUPPORTING DOCUMENTS:

A. DMF:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
[REDACTED]	IV	[REDACTED]	[REDACTED]	1 & 5	Adequate	04-MAR-2009	N21-368, Cialis [®] Tablet, 20mg

b(4)

¹Action codes for DMF Table:
 1--DMF Reviewed
 Other codes indicate why the DMF was not reviewed, as follows:
 2--Type 1 DMF
 3--Reviewed previously and no revision since last review
 4--Sufficient information in application
 5--Authority to reference not granted
 6--DMF not available
 7--Other (explain under "Comments")

²Adequate, Inadequate

B. Other Documents:

NDA # or IND #	Applicant	Drug Product	Approval Date or Active Date
I71,871	Eli Lilly	Adcirca™ (tadalafil) Tablet	6/18/2005
N21-368	Eli Lilly	Cialis® (tadalafil) Tablet	11/21/2003

17. STATUS:

Reviews	Recommendation	Date	Reviewer
EES	Acceptable	06-NOV-2008	Office of Compliance
Medical	<i>pending</i>	<i>n/a</i>	Dr. Gordon
Pharm/Tox	Approval	06-MAR-2009	Dr. Koerner
Clinical Pharmacology	<i>pending</i>	<i>n/a</i>	Dr. Younis
Environmental Assessment	Acceptable	10-MAR-2009	Donald Klein, Ph.D.



The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 22-332 for Adcirca™ (tadalafil) Tablet is recommended approval for CMC.

B. Recommendations on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

The Adcirca™ Tablet (20 mg) consists of the same core tablet shape and the same components as the approved 20 mg Cialis® Tablet. Furthermore, the 20 mg Adcirca™ Tablet is manufactured and monitored (process controls) by the same process as the approved Cialis® 20 mg Tablet. The difference between the proposed 20 mg Adcirca™ Tablet and the approved 20 mg Cialis® Tablet is the debossment and the film coating color.

Debossment:

20 mg Adcirca™ Tablet: **4467**

20 mg Cialis® Tablet: **C20**

Film Coating Color:

20 mg Adcirca™ Tablet: Orange color (same formulation as the Cialis® 20 mg tablet but with the

20 mg Cialis® Tablet: color.

CHEMISTRY REVIEW

As a result of the Filing meeting discussion, the review team questioned the applicant about the availability of a 40 mg Adcirca™ tablet, and Eli Lilly stated there is no intention of manufacturing a 40 mg dosage strength.

The formulations used in the NDA 22-332 Adcirca™ clinical trials were identical to the commercial Cialis® (tadalafil) Tablets (2.5 mg, 10 mg, and 20 mg). Eli Lilly provided all the pertinent clinical trial CMC data. Each clinical trial batch met the approved Specifications.

With respect to the 1/15/08 Pre-NDA meeting agreed CMC items, Eli Lilly adhered to the batch size (3 batches of _____ tablets) and to the amount of stability data (primary and supportive) submitted with the original submission. In addition, Eli Lilly provided updated stability data during the review cycle as was discussed at the Pre-NDA meeting.

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Adcirca™ Tablet (20 mg) Specifications are identical to the approved N21-368 Cialis® (tadalafil) Tablet (20 mg) Specifications with the exception of the **Appearance Specification** and the deletion of the _____ (Karl Fischer) Specification. Each Adcirca™ Tablet (20 mg) drug product batch (3) met the proposed Specifications and each batch was placed on stability testing. Regarding the stability testing of the Adcirca™ Tablet (20 mg), Eli Lilly is monitoring the _____

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Because the Adcirca™ Tablet (20 mg) has the _____ excipient, the following four, approved, NDA 21-368 analytical procedures were validated to ensure that the new excipient _____ did not have a deleterious impact (interference) on the respective test methods: **Rate of Release** (B06649); **Content Uniformity** (B07017); **Identification** (B07358); and **Related Substances** (B07000). Each test method was found acceptable.

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Based on Eli Lilly's 3/9/09 response, the 75 mL, white, _____ bottle is the marketed package and will contain 60 tablets.

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CHEMISTRY REVIEW

A 36 month Expiry is granted for the Adcirca™ Tablet (20 mg) based on the stability data results (primary and supportive).

Three drug product sites were submitted to Compliance via EES. The Office of Compliance issued an overall recommendation of acceptable on 11/6/08.

Drug Substance

The drug substance section of NDA 21-368, Cialis® (tadalafil) Tablet (approved 11/21/2003) is referenced.

The drug substance lots used in the clinical trials were correlated with the drug product lots (TABLE 4 (CMC Manufacturing Information for Clinical Trial Lots)).

Two drug substance sites were submitted to Compliance via EES. The Office of Compliance issued an overall recommendation of acceptable on 11/6/08.

B. Description of How the Drug Product is Intended to be Used:

The patient is instructed to take 2 x 20 mg Adcirca™ Tablet per day.

The Adcirca™ Tablet (20 mg) will be packaged in a rectangular, white, _____
_____ 75 ml bottle with either a child-resistant closure _____
_____. Sixty (60)
tablets will be present in the 75 mL bottle.

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Based on the photostability testing results the Adcirca™ Tablet (20 mg) does not require special labeling or packaging requirements.

C. Basis for Approvable or Not-Approval Recommendation:

NDA 22-332 (Adcirca™ Tablet, Eli Lilly and Company) is recommended approval.



CHEMISTRY REVIEW



D. Administrative:

ONDQA Reviewer, Branch VII: Donald N. Klein, Ph.D.

ONDQA PAL, Branch VII: Ramesh Raghavachari, Ph.D.

ONDQA Branch Chief, Branch VII: James Vidra, Ph.D.

ONDQA Project Manager, Branch VII: Teshara Bouie.

OND Project Manager, HFD-110: Dan Brum.

37 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Donald Klein
3/10/2009 09:40:47 AM
CHEMIST

Goal date is 5/24/09; OND requested reviews be completed
by 3/15/09.

Jim Vidra
3/10/2009 03:20:18 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-332
Applicant:	Eli Lilly & Co.
Letter Date:	23 July 2008
Stamp Date:	24 July 2008
PDUFA Date:	24 May 2009
Tradename:	Adcirca
Established Name:	Tadalafil
Dosage Form:	Tablets, 20 mg
Route of Administration:	Oral
Indication:	Pulmonary arterial hypertension
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

Summary

This is a Type 6 NDA in e-CTD format for tadalafil tablets which was approved under the tradename Cialis on Nov. 21, 2003 for the treatment of erectile dysfunction (NDA 21-368, Division of Urologic and Reproductive Drug Products). The new indication is for pulmonary arterial hypertension and clinical development for this was carried out under IND 71,871. A multidisciplinary pre-NDA meeting was held on Jan.15, 2008 to discuss the format and content of the NDA submission. It was agreed that 3 months' stability data for Adcirca tablets at the time of NDA submission would be acceptable in view of the similarity of this product to Cialis. Stability updates would be available during the review period. Lilly was asked to submit 24 months of long term data and 6 months accelerated data for Cialis for comparison.

Drug Substance

There have been no changes to the drug substance, tadalafil, and all CMC information is by reference to NDA 21-368.

Drug Product

Adcirca will be available as 20 mg immediate release tablets. These tablets consist of the same core tablet shape and components and are manufactured by the same process as the approved Cialis 20 mg tablets. The differences are in the debossment and the film coating which imparts an orange color to Adcirca instead of the yellow color of Cialis, 20 mg. Two types of in-process controls have been defined: _____

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Proven Acceptable Ranges have been given for the critical process parameters and the criteria for forward processing. The specification for Adcirca tablets is stated to be identical to that of Cialis with the exception of physical appearance and deletion of the test for _____. The container closure for Adcirca will be white _____ bottles with plastic child resistant screw caps and aluminum foil induction heat seal liners. This is the same as for Cialis. Primary stability studies are on-going for 3 lots of Adcirca manufactured at 1/10th the commercial scale and 3

b(4)

months' data are provided at long term and accelerated conditions. A shelf life of 36 months is proposed.

Critical Review Issues

Drug Product

- Lilly has introduced some QbD concepts in the manufacturing process – ~~_____~~ which should be reviewed and evaluated. This may be new to this application since the CMC review of Cialis did not cover this information.
- Is omission of testing for ~~_____~~ specification justified?
- Why is stability in ~~_____~~ being performed if only the bottle configuration is proposed for marketing?

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Comments and Recommendations

The application is fileable. Manufacturing, testing and packaging facilities have been entered into EES and the reviewer should verify the accuracy and completeness of the entries. It should be noted that there are two CFN numbers for the same address of the ~~_____~~ facility; the CFN number for the drug product manufacturing facility was not provided in the NDA but was retrieved from an efficacy supplement to NDA 21-368. A single CMC reviewer, preferably one with some experience in QbD, is recommended for this application.

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Kasturi Srinivasachar
Pharmaceutical Assessment Lead
Ramesh Sood, Ph.D.
Branch Chief

July 28, 2008
Date
July 28, 2008
Date

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

/s/

Kasturi Srinivasachar
7/28/2008 02:55:21 PM
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Ramesh Sood
7/29/2008 12:29:45 PM
CHEMIST