NDA 21-368

Cialis
Tadalafil tablets

Lilly ICOS LLC

Rajiv Agarwal, Ph.D

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
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1. NDA #: 21-368
2. REVIEW #: 3
3. REVIEW DATE: 20-NOV-2003
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS:

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7. NAME & ADDRESS OF APPLICANT:

Name: Lilly ICOS LLC
Address: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285
Representative: Ms. Catherine A. Melfi, Ph.D
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Cialis
   b) Non-Proprietary Name (USAN): Tadalafil
   c) Code Name/# (ONDC only): IC351, LY450190
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 1
      - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Phosphodiesterase Type 5 inhibitor/ Erectile Dysfunction

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5, 10 and 20 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
   - ___SPOTS product – Form Completed
   - _x_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

   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-1, (6R, 12aR)-

   ![Chemical Structure Diagram]

Page 5 of 31
Molecular Formula: C_{22}H_{19}N_{3}O_{4}
Molecular weight: 389.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Refer to CMC reviews #1 and 2 dated 27-FEB-2002 and 29-APR-2002, respectively.

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1 Action 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”)

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:
- Chemistry Review #2 dated 29-APR-2002
- Teleconference minutes dated 26-NOV-2002 and 15-DEC-2002

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The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA may be APPROVED from the CMC point of view.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product:

Cialis (tadalafil), 5, 10 and 20 mg tablets are almond shaped, and film-coated tablets and depending on strength, tablets have varying shades of yellow. Tablets are also debossed on one side with “C 5”, “C 10” or “C 20” to reflect strengths. The primary stability and clinical batches of the Cialis tablets are manufactured, packaged, and tested by Eli Lilly in Indianapolis (Indiana). However, the tablets are also manufactured, tested and packaged in Carolina, Puerto Rico. The tablets manufactured at Carolina, PR are comparable to tablets manufactured at Indianapolis, IN as evident by the comparative Certificate of Analysis and dissolution profiles.

Due to continued non-compliance with cGMP, applicant withdrew the manufacturing site in Indianapolis from the application on 20-OCT-2003. The alternative site in Carolina, Puerto Rico is in compliance with cGMP.

The tadalafil is incorporated into a to consistently produce tablets with good homogeneity and the desired dissolution characteristics. The quality of the tablets is controlled by tests: appearance, identification, assay, uniformity of dosage unit, total related substances, individual related substances, water and dissolution. The proposed time-points of dissolution acceptance criterion are deemed adequate after acceptance criterion at 30 min. was tightened to Q%=%

All the test methods and respective acceptance criteria are satisfactory except for the "Individual related substance (LIRS)" and "Total related substances (TRS)". Applicant proposed to re-evaluate the acceptance criteria for the "Largest individual related substance" and "Total related substances" after sufficient experience is gained. Since the toxicologist in the division confirmed that the proposed limit is within the qualified level, the proposal is accepted. Post approval stability commitment has been satisfactorily revised as requested by the division.

The tablets will be marketed in bottle configurations containing 30 tablets, respectively. Tablets in bottles are samples for physician and tablets in 30 count bottles are for pharmacy. All packaging components are adequate for protecting the drug product during the shelf life.
Based on the updated stability data on primary stability batches, ___ of expiration dates is granted for the ___
While, ___ of expiration dates is granted for the ___

The trade name “Cialis” has been accepted by DMETS (25-SEP-2003). Applicant has accepted the division’s proposal to use ___ bottle (physician sample for 10 mg and 20 mg tablets) and indicated that an appropriate container will be provided by the pharmacist to fill the prescription from ___ bottle. Per our recommendation, storage statement is revised and dosage form is indicated in both the physician insert and labels after established name. Primary container/closure labels for bottles are provided for all three strengths and revised according to the recommendations.

Drug Substance:

Tadalafil is a new molecular entity and is manufactured by Eli Lilly and Company in Lafayette (Indiana). Tadalafil structure includes two asymmetric chiral centers but X-ray studies indicate that only ___ is present in the drug substance. Tadalafil has an unusually high melting point ___ and is practically insoluble in water ___ but is very soluble in ethanol and classified as a low soluble and highly permeable drug ___. This suggests that tadalafil is a compound in the Biopharmaceutics Drug Classification system ___ of tadalafil is obtained by ___ from ___ This form is most thermodynamically stable form in aqueous solutions and is the least soluble form in water. The drug substance is non-hygrosopic. The tadalafil is ___ and is in compliance with cGMP. The rate of release of tadalafil from the core tablets increases with decreasing particle size. The particle size is controlled by ___ to provide a particle size for ___ of the drug substance ___ and the particle size specification has been established at NMT ___ as measured by ___

The quality of the tadalafil is controlled by specification set by the manufacturer, which includes, identity by ___ identity by ___ HPLC, assay, related substances (excluding ___

All the test methods and respective acceptance criteria are satisfactory.

Eli Lilly manufacturing site in Lafayette, IN, is in compliance with cGMP.

Based on the updated stability information, ___ of the re-test period is granted.

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

This product is indicated for erectile dysfunction based on potent, selective, reversible inhibition of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5.
The recommended starting dose of CIALIS in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.
C. Basis for Approvability or Not-Approval Recommendation

- Outstanding issues from Chemistry Review # 1 (dated 27-FEB-2002) and # 2 (dated 29-APR-2002) of NDA 21-368 have been satisfactorily resolved.
- The final recommendation from the Office of Compliance on the manufacturing, packaging and control testing sites is “Acceptable” (See Appendix-1).

III. Administrative

A. Reviewer’s Signature Electronically captured in DFS

B. Endorsement Block

HFD-580/RAgarwal/ MRhee/ FDeguia/JMercier/ Date: 20-NOV-2003

C. CC Block

HFD-820/EDuffy/Duu Gong Wu
page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.
generally <10% of glucuronide concentrations. The catechol, methylcatechol, and methylcatechol glucuronide (LY559171) metabolites were evaluated in vitro for potency and selectivity against PDEs. The catechol and methylcatechol were highly selective for PDE5, when compared with the other PDEs, but were 45-fold and 230-fold less potent for PDE5, respectively, compared with tadalafil. The methylcatechol glucuronide was not selective for PDE5 and was at least 13,000-fold less potent for PDE5 than tadalafil. Since this metabolite is primarily cleared by the renal route, in moderate renal impairment the exposure to methylcatechol glucuronide was 3.6-fold higher. This patient population also had higher incidence of musculoskeletal adverse events such as myalgia and back pain. The onset of these adverse events generally occurs approximately 20 hours after peak plasma concentrations of tadalafil, and when the methylcatechol glucuronide concentrations are high. Due to the increased incidence of adverse events in moderately impaired subjects, no subjects with severe renal impairment received tadalafil. In another study comparing elderly and young subjects, clearance was reduced by approximately 20% in the elderly subjects. Two (17%) elderly subjects (but no young subjects) reported a total of three severe adverse events (one episode of pain and two episodes of myalgia) that were related to the study drug. Creatinine clearance was approximately 17% lower in the elderly subjects.

Tadalafil pharmacokinetics in patients with erectile dysfunction are essentially similar to pharmacokinetics in healthy subjects. Systemic exposure of tadalafil was reduced by almost 20% in subjects with diabetes. AUC increased in a dose proportional manner across the 2.5 to 20 mg dose range, whereas increase in \( C_{\text{max}} \) was less than dose proportional at doses higher than 10 mg. Steady-state plasma concentrations are attained by Day 5 and are approximately 1.6-fold higher than the single dose values. Concentrations of methylcatechol glucuronide were approximately 3-fold higher than single dose values. In vitro studies suggested that, tadalafil is predominantly metabolized by CYP3A4. Ketoconazole, a selective inhibitor of CYP3A4, increased tadalafil exposure by 107%. Rifampin, a CYP3A4 inducer, reduced tadalafil AUC by 88%. Results with cultured human hepatocytes indicated that tadalafil produces both mechanism-based inhibition of CYP3A activity and induction of CYP3A protein expression. Tadalafil inhibited the catalytic activities for CYP1A2, CYP2C9, and CYP3A, with apparent \( K_i \) values of \( * \), respectively. Once-daily administration of 20 mg tadalafil for 10 days resulted in a mean \( C_{\text{max}} \) value of \( * \), the highest individual plasma concentration was 785 \( \mu \)g/L (2.02 \( \mu \)M). With tadalafil concentration of 2.02 \( \mu \)M at the active site of the enzymes, the projected in vivo inhibition of metabolism mediated by CYP3A4, CYP2C9, and CYP1A2 was 4.7%, 3.0%, and 12.8%, respectively. The \( I/K_i \) ratio for CYP3A4 was 0.05, which indicated that the likelihood of an interaction is remote. Daily dosing of 10 mg tadalafil for 14 days resulted in small reduction in AUC (13%) and increase in CL/F (14%) for midazolam. This effect may be even more pronounced with a higher dose tadalafil.

Tadalafil undergoes extensive metabolism in the liver. Thus, hepatic impairment is expected to reduce the metabolic clearance of tadalafil. However, mild and moderate hepatic impairment did not compromise metabolic clearance of tadalafil and systemic exposure (AUC) to tadalafil was similar across subject groups. On the other hand,
systemic exposure was ~2-fold higher in subjects with mild and moderate renal impairment. Renal impairment had a greater effect on the disposition of methylcatechol glucuronide than on tadalafil, as expected for a renally-cleared metabolite. Mean AUC of total IC710 (methylcatechol glucuronide) was approximately 3.6-fold and 2.2-fold higher in moderate and mild renally impaired subjects, respectively. Due to the increased incidence of adverse events in moderately impaired subjects, no subjects with severe renal impairment received tadalafil.

Pharmacodynamic drug-drug interaction studies were conducted with drugs that are likely to be co-administered with tadalafil. Interaction studies with nizatidine, Maalox, theophylline, warfarin, metoprolol, bendrofluazide, enalapril, Aspirin, isosorbide mononitrate, and sublingual nitroglycerin used only 10 mg tadalafil. Studies with lovastatin, angiotensin II receptor antagonists, and tamsulosin (PD) were conducted in presence of 20 mg tadalafil. Both 10 mg and 20 mg doses of tadalafil were used to investigate interaction with alcohol and the calcium channel blocker, amiodipine. More drug-related adverse effects were observed when each of these drugs were administered with tadalafil than with placebo. However, only clear evidence of significant pharmacodynamic interaction was noted with 20 mg tadalafil in chronically administered angiotensin AT1 receptor antagonists in hypertensive subjects, based on ambulatory systolic blood pressure.

Following co-administration of 10 mg tadalafil with 0.7 mg/kg alcohol, there were trends for greater impairment of some parameters (postural stability and word recognition), larger decrease in mean standing diastolic blood pressure (~12 mmHg at 4 hr), and greater increase in heart rate compared to the administration of alcohol with tadalafil placebo. In addition, the overall incidence of adverse events was highest following administration of tadalafil with alcohol compared to other combinations. In another study conducted in 48 male subjects to investigate the pharmacodynamic interaction between alcohol and 20 mg tadalafil clinically significant interaction was not observed. However, the dose level of alcohol used in this study was lower (0.6 g/kg). In the previous study, an oral dose of 0.7 g/kg resulted in blood levels (80 mg/dL) that correspond to legal intoxication as defined in the UK and in several states in the USA. The sponsor did not measure alcohol blood levels in the study conducted with 20 mg tadalafil.

Tadalafil potentiates the hypotensive effect of organic nitrates. A similar number of subjects had clinically significant changes in standing systolic and diastolic blood pressure following administration of 0.4 mg sublingual nitroglycerin with 10 mg tadalafil and with 50 mg sildenafil, the frequency of which was generally up to two-fold higher than for nitrate administered with placebo.

Population analyses were conducted in three Phase 2 studies (LVAC, LVBF and LVBG), and in one Phase 3 trial (CSR.LVCE). Response scores to IIEF Question 3 and Question 4 were used as endpoints in all three phase 2 studies. The pharmacodynamic model was based on the pharmacologically relevant E\textsubscript{max} model describing a saturable drug response with increasing dose. Based on the results of these studies, it appears that the probability
APPENDIX-I

18-NOV-2003

FDA CDER RES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: MDA 21368/000
Stamp: 29-JUN-2001
Regulatory Due: 28-NOV-2003
Applicant: LILLY ICOS
Address: LILLY CORPORATE CENTER
INDIANAPOLIS, IN 45285
Priority: 18
Org Code: 580

Action Goal: 29-SEP-2003
District Goal: CIALIS (TADALAFIL) 20MG
Brand Name: TADALAFIL
Generic Name: TABLETS
Dosage Form: TABLET
Strength: 5 MG, 10 MG, 20 MG

Application Comment: THIS IS AN NEW COMPOUND WHICH WILL BE FORMULATED INTO A 20 MG TABLET. (on 23-AUG-2001 by D. LIN (HPD-830) 301-827-2049)

FDA Contacts:
N. AGARWAL
Review Chemist
(HFD-580) 301-827-4237

M. RAKER
Team Leader

Overall Recommendation:
ACCEPTABLE on 13-NOV-2003 by S. ADAMS (HPD-322) 301-827-9051
WITHOLD on 25-AUG-2003 by J. D AMBROGIO (HPD-122) 301-827-9049
WITHOLD on 17-JUN-2002 by J. D AMBROGIO (HPD-122) 301-827-9049
WITHOLD on 29-APR-2002 by J. D AMBROGIO (HPD-122) 301-827-9049

Establishment: CMH 1813682
ELI LILLY CO/TIPPECANOE
BOX 685 LILLY RD
LAFAYETTE, IN 47902

DMF No:

Responsibilities:
AADA:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile:
CSN OAI Status: NONE

Establish. Comment:
DRUG SUBSTANCE MANUFACTURER. (on 23-AUG-2001 by D. LIN (HPD-830) 301-827-2049)

Milestone Name
Date Type Insp. Date Decision & Reason Creator

SUBMITTED TO OC 23-AUG-2001 LUDAY
SUBMITTED TO DO 23-AUG-2001 PS AMBROGIOJ
ASSIGNED INSPECTION 25-NOV-2001 PS MROBINSON
INSPECTION SCHEDULED 11-DEC-2001 15-FEB-2002 MROBINSON
INSPECTION SCHEDULED 07-FEB-2002 29-MAR-2002 MROBINSON
INSPECTION SCHEDULED 13-MAR-2002 26-APR-2002 MROBINSON
INSPECTION PERFORMED 18-APR-2002 18-APR-2002 MROBINSON

RIR 4/1-18/2002 WILL BE CLASSIFIED VAI.
INSPECTION PERFORMED 18-APR-2002 18-APR-2002 MROBINSON

This was a drug pre-approval, follow-up and cGMP inspection of a large API manufacturer.
APPEARS THIS WAY ON ORIGINAL

18-NOV-2003

FDA CDER ERS
ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

DO RECOMMENDATION 29-APR-2002

EIR 4/1-18/2002 WILL BE CLASSIFIED VAI.
OC RECOMMENDATION 29-APR-2002

DO RECOMMENDATION 28-MAY-2002

EIR 4-1-18/02 WAS CLASSIFIED VAI.
OC RECOMMENDATION 28-MAY-2002

SUBMITTED TO OC 11-JUN-2003
OC RECOMMENDATION 11-JUN-2003

ACCEPTABLE MBROBINS
INSPECTION

ACCEPTABLE NADAMOGIOJ
DISTRICT RECOMMENDATION

ACCEPTABLE MBROBINS
INSPECTION

ACCEPTABLE NADAMOGIOJ
DISTRICT RECOMMENDATION

ACCEPTABLE NAADAMS
DISTRICT RECOMMENDATION

ACCEPTABLE NAADAMS
BASED ON PROFILE

Establishment: CPN 2619243
ELI LILLY INDUSTRIES INC
126 FM 65TH INFANTRY RD
CAROLINA, PR 00985

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### Chemistry Review Data Sheet

**APPEARS THIS WAY ON ORIGINAL**

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**DMF No:**

**Responsibilities:**

**Profile:** TCM

**OAI Status:** NONE

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*Based on file review*

*District recommendation*
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/s/
Rajiv Agarwal
11/20/03 12:58:06 PM
CHEMIST

Moo-Jhong Rhee
11/20/03 01:16:56 PM
CHEMIST
I concur
NDA 21-368

CIALIS (tadalafil) 5, 10, 20 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Lily ICOS LLC
[Joint venture between Lilly and ICOS]

Indication: For treatment of erectile dysfunction.

Presentations: __ bottles.

EER Status: Acceptable 13-NOV-2003

Consults: OCPB - dissolution test is acceptable
DMETS - CIALIS is acceptable
Statistics - recommendations re statistical treatment of matrixing approach provided

CIALIS was submitted 28-JUN-2001

The drug substance is manufactured by Lilly at the Lafayette IN site - CGMP compliant. Drug substance characterization and manufacturing are adequate. —

CGMP compliant.

Specifications are considered adequate with the exception of impurities, which the sponsor has agreed to re-evaluate after additional manufacturing experience is gained. The specifications will be established —-: A re-test period of — months is supported by submitted stability data.

Conclusion
Drug substance is acceptable.

The drug product is a 10 and 20 mg film coated tablet. The product will be manufactured at the Lilly Carolina, Puerto Rico site. The Indianapolis site has been withdrawn. The manufacturing process and controls are considered acceptable. Specifications are considered adequate with the exception of impurities which the sponsor has agreed to re-evaluate after additional manufacturing experience is gained. The specifications will be finalized within 1 year. Expiry of 24 months supported by submitted stability data. Labels and labeling are acceptable.

All associated DMFs are acceptable.

Conclusion
Drug product is acceptable
Overall Conclusion
From a CMC perspective the application is recommended for an approval action.

Eric P Duffy, PhD
Director, DNDC II/ONDC
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/s/

Eric Duffy
11/20/03 04:40:02 PM
CHEMIST
CIALIS (tadalafil) 10, 20 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Lily ICOS LLC
[Joint venture between Lilly and ICOS]

Indication: For treatment of erectile dysfunction.

Presentations:  — bottles ————


Consults: OCPB - no review provided
OPDRA - no review provided – CIALIS is acceptable
Statistics - recommendations re statistical treatment of matrixing approach provided

CIALIS was submitted 28-JUN-2001. A IR letter was issued 11-FEB-2002, and was responded to in the amendment dated 6-MAR-2002.

The drug substance is manufactured by Lilly at the Lafayette IN site – 483 was issued. Drug substance characterization and manufacturing are adequate. __________ performed by ____________________ - compliance OK. Specification are considered adequate with the exception of impurities, which the sponsor has agreed to re-evaluate after additional manufacturing experience is gained. A re-test period of ———— is supported by submitted stability data.

Conclusion
Drug substance is acceptable.

The drug product is a 10 and 20 mg __________ tablet. The product is manufactured at the Lilly Indianapolis site – 483 issued. The manufacturing process and controls are considered acceptable. Specifications are considered adequate with the exception of impurities which the sponsor has agreed to re-evaluate after additional manufacturing experience is gained. Expiry of 24 months supported by submitted stability data.

All associated DMFs are acceptable.

Overall Conclusion
From a CMC perspective the application is recommended for an approvable action.
Eric P Duffy, PhD
Director, DNDC II/ONDC
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/s/

Eric Duffy
5/13/02 10:28:18 AM
CHEMIST
CMC Div Director review - thought this had already been signed off.
NDA 21-368

Cialis
Tadalafil tablets

Lilly ICOS LLC

Rajiv Agarwal, Ph.D

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
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Chemistry Review Data Sheet

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3. REVIEW DATE: 29-APR-2002
4. REVIEWER: Rajiv Agarwal
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7. NAME & ADDRESS OF APPLICANT:

Name: Lilly ICOS LLC
Address: 1209 Orange Street, Wilmington, DE 19801
Representative: Dr. Gregory T. Brophy
Telephone: 317-277-3799

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cialis
b) Non-Proprietary Name (USAN): Tadalafil
c) Code Name/# (ONDC only): IC351, LY450190
d) Chem. Type/Submission Priority (ONDC only):
9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Phosphodiesterase Type 5 inhibitor/ Erectile Dysfunction

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:
   ______SPOTS product – Form Completed
   ___x_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

   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-, (6R, 12aR)-

   Molecular Formula:  C_{22}H_{19}N_{1}O_{4}
Molecular weight: 389.41

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1 Action 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")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

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The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is approvable from the CMC point of view.

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

Based on the ICH-Q6A (decision tree # 1 and # 2), applicant is asked to tighten the proposed acceptance criteria for impurities identified in the drug substance and drug product. In an amendment, 06-MAR-2002, submitted in response to the IR letter dated 11-FEB-2002, applicant requests that at this time, it would be inappropriate to set acceptance criteria that may be too tight and a “re-evaluation of the acceptance limits of impurities will be performed when sufficient production experience has been gained in the case of both drug substance and drug product”.

The division accepts the request. Based on their experience in the production of drug substance and drug product, the applicant should notify the division of their final acceptance criteria within ———— from the action date (approval date).

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product:

CIALIS (tadalafil), 20 mg, is an ———— tablet, which is yellow, almond shaped, film coated and debossed on one side with “C20”. This product is indicated for erectile dysfunction based on potent, selective, reversible inhibition of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. The Cialis tablets are manufactured, packaged, and tested by Eli Lilly in Indianapolis (Indiana).

Inspection of the drug product manufacturing site has disclosed continued non-compliance with cGMP, therefore, the final recommendation from the Office of Compliance for the Eli Lilly manufacturing site is “Withhold”.

The quality of the tablets is controlled by tests: appearance, identification, assay, uniformity of dosage unit, total related substances, largest individual related substances, water and dissolution. ————time-point of dissolution acceptance criterion are deemed adequate. All the test methods and respective acceptance criteria are deemed satisfactory except for the ‘ ———— ’ and ‘ ———— ’

Applicant proposed to re-evaluate the acceptance criteria for the “Largest individual related substance” and “Total related substances” after sufficient experience is gained. Since the toxicologist in the division confirmed that the proposed limit is within the qualified level, the proposal is accepted. Post approval stability commitment has been satisfactorily revised as requested by the division.

The tablets will be marketed in ———— bottle configurations containing ———— 30 tablets, respectively. Tablets (20 mg) in ———— bottles are for physician samples only.
Product: Cialis

Applicant: Lilly ICOS

and tablets in 30 count bottles are for Pharmacy. All packaging components are deemed adequate for protecting the drug product during the shelf life.

Based on the stability studies (12 months at long term and 6 months at accelerated testing conditions) on primary batches, 18-month of expiration date can be granted for the 20 mg tablets packaged in bottles and blister.

The trade name “Cialis” has been accepted by OPDRA. Applicant has accepted the division’s proposal to bottle (physician’s sample) and indicated that an appropriate container will be provided by the pharmacist to fill the prescription from bottle. Per our recommendation, storage statement is revised and dosage form is indicated in both the physician insert and labels after established name. Primary and secondary container/closure labels for both bottles

However, there were some minor comments from OPDRA, of which clarification with the applicant will be deferred to next review cycle.

Drug Substance:

Tadalafil is a new molecular entity and is manufactured by Eli Lilly and Company in Lafayette (Indiana). Tadalafil structure includes two asymmetric chiral centers but X-ray studies indicate that only is present in the drug substance. Tadalafil has an unusually high melting point and is practically insoluble in water but is shown to be soluble in DMSO. A form of tadalafil is obtained by and is in compliance with cGMP.

The quality of the tadalafil is controlled by specification set by the manufacturer, which includes, identity by IR, identity by HPLC, assay, related substances (excluding chiral impurities),

They are deemed satisfactory. All the test methods and respective acceptance criteria are deemed satisfactory except for the acceptance criteria of impurities as discussed earlier.

The final recommendation from the Office of Compliance for Eli Lilly manufacturing site is “acceptable”.

Based on the updated stability information, can be granted.

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

The proposed dose of CIALIS is 20 mg and is taken orally prior to anticipated sexual activity without regard to food. The maximum recommended dosing frequency is once a day.

C. Basis for Approvability or Not-Approval Recommendation

- Outstanding issues from Chemistry Review # 1 of NDA 21-368 has been satisfactorily resolved (see attached Chemistry Review notes).
- There were some comments from OPDRA which need to be clarified with the applicant (see OPDRA review dated 19-APR-2002 and page 20 of this review).
- Inspection of the drug product manufacturing site has disclosed continued non-compliance with cGMP, therefore, the final recommendation from the Office of Compliance for the Eli Lilly site is “Withhold” (see Appendix-1).
III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/RAgarwal/ MRhee/ D Spell Le-Sane/ Date: 29-APR-2002

C. CC Block

HFD-820/EDuffy/Duu Gong Wu
13 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.
APPENDIX-I

29-APR-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21368/000
Stamp: 29-JUN-2001
Regulatory Due: 29-APR-2002
Application Comment: This is an NHEP associated with a 20 mg
Strength: TABLET
Dosage Form: TABLET

Action Goal: D1 - FEB-2002
District Goal: D1 - FEB-2002
Brand Name: CIALIS (TADALAFIL) 20 MG
Generic Name: TADALAFIL

Applicant: Lilly ICOS
Established Name: Lilly Corporate Center
ININDIANAPOLIS, IN 46285
Priority: 10
Org Code: 580

FDA Contacts: R. Agaikal, Review Chemist
M. Radz (HYD-580) 301-827-4237, Team Leader

Overall Recommendation: WITHHELD on 29-APR-2002 by J. D Ambrigio (HYD-324) 301-827-0063
Establishment: 1813670
ELI LILLY AND CO
LILLY CORP CTR/WIHITE RIVER PRT/EAST DA
INDIANAPOLIS, IN 46206

ORI No: DAA;
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: TCN
AQT Status: OAI ALERT
Estab. Comment: DRUG PRODUCT MANUFACTURER AND SITE OF STABILITY TESTING. (on 23-
AUG-2001 by D. Lim (HYD-580) 301-827-4230)

Milestone Name | Date | Req. Type/Inspection Date | Decision & Reason
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SUBMITTED TO OC | 23-AUG-2001 FS | | WITHHELD
DO RECOMMENDATION | 23-APR-2002 | | WITHHELD

PREVIOUS PROFILE IS CLASSIFIED NOT ACCEPTABLE. A GAP INSPECTION IS IN
PROGRESS BUT WILL NOT BE COMPLETED BY 4/29/2002. DETROIT DISTRICT CANNOT
MAKE A FINAL RECOMMENDATION UNTIL EI IS COMPLETED.

OC RECOMMENDATION 23-APR-2002
WITHHELD

Establishment: 1813662
ELI LILLY CO/TIPPECANOE
BOX 665 LILLY RD
LAFAYETTE, IN 47902

ORI No: AADA;
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE STABILITY TESTER

Profile: CSH
AQT Status: NONE
29-APR-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Estab. Comment: DRUG SUBSTANCE MANUFACTURER. (on 23-AUG-2001 by D. LIN (HFD-580) 301-827-4230)

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DHF No: _____________________________

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Profile: CRU                      OAI Status: NONE

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/s/

Rajiv Agarwal
4/29/02 11:44:38 AM
CHEMIST

Moo-Jhong Rhee
4/29/02 11:55:47 AM
CHEMIST
I concur
NDA 21-368

Cialis
Tadalafil tablets

Lilly ICOS LLC

Rajiv Agarwal

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
1. NDA #: 21-368
2. REVIEW #: 1
3. REVIEW DATE: 26-FEB-2002
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

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7. NAME & ADDRESS OF APPLICANT:

Name: Lilly ICOS LLC
Address: 1209 Orange Street, Wilmington, DE 19801
Representative: Dr. Gregory T. Brophy
Telephone: 317-277-3799

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cialis
b) Non-Proprietary Name (USAN): Tadalafil
c) Code Name/# (ONDC only): IC351, LY450190
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type: 1
   - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Phosphodiesterase Type 5 inhibitor/ Erectile Dysfunction

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _x_Rx   ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:
   ___SPOTS product – Form Completed
   _x_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

   ![Chemical Structure Image]

   **Molecular Formula:** C_{22}H_{19}N_{3}O_{4}

   **Molecular weight:** 389.41

17. RELATED/SUPPORTING DOCUMENTS:

   A. DMFs:

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Page 3 of 60
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<td>2 – Type 1 DMF</td>
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<td>3 – Reviewed previously and no revision since last review</td>
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4 – Sufficient information in application  
5 – Authority to reference not granted  
6 – DMF not available  
7 – Other (explain under "Comments")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:  
- IND 54,553  
- IND  
- Patent # 5,859,006 for compound (expiry date 12-JAN-2016)  
- Patent # 6,140,329 for method of use (expiry date 11-JUL-2016)  
- Filing meeting minutes 20-AUG-2001

18. STATUS:

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The Chemistry Review for NDA 21-368

Page 5 of 60
The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is approvable.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product:

CIALIS (tadalafil), 20 mg, is an --- tablet, which is yellow, almond shaped, film coated and debossed on one side with “C20”. This product is indicated for erectile dysfunction based on potent, selective, reversible inhibition of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. The Cialis tablets are manufactured, packaged, and tested by Eli Lilly in Indianapolis (Indiana). The final recommendation from the Office of Compliance for the Eli Lilly site is still pending.

The quality of the tablets is controlled by tests: appearance, identification, assay, uniformity of dosage unit, totals related substances, largest individual related substances, water and dissolution. All the respective acceptance criteria are deemed satisfactory except for the acceptance criteria of impurities. It should be further tightened, unless justified.

The tablets are packaged in

---

The tablets (10 tablets).

---

Sponsor is requesting a 24 months of shelf life. Based on the stability studies on primary batches, 18 months of expiry date can be granted for the product packaged in bottles ---. Moreover, the post approval stability commitment is not satisfactory and needs to be further revised.

To validate the analytical procedures, applicant is asked to submit three copies of method validation package.
The trade name “Cialis” has been accepted by OPDRA, and adequate chemistry information is presented in the labeling. However, the statement in How supplied section, as well the storage statement should be revised as delineated in draft deficiency letter and a warning statement “

Additionally, the dosage form “tablets” should be added to both physician insert and labels after established name. The labels for bottles:

Drug Substance:

Tadalafil is a new molecular entity and is manufactured by Eli Lilly and Company in Lafayette (Indiana). The final recommendation from the Office of Compliance for Eli Lilly site is still pending.

The quality of the tadalafil is controlled by specification set by the manufacturer, which includes, identity by IR, identity by HPLC. assay related substances (excluding chiral impurities).

They are deemed satisfactory. All the respective acceptance criteria are deemed satisfactory except for the acceptance criteria of impurities. It should be further tightened, unless justified.

To further ensure the quality of the drug substance, a reference standard of highest purity is warranted. Therefore, a summary of manufacturing, characterization, analytical testing, COA and storage information is requested.

The bulk drug substance will be stored in the and it is deemed necessary to have it tested for its suitability as a container. Therefore, results of test are requested.

Microbial testing and limits are not included, therefore, applicant is asked to justify for not providing microbial limit specification.

Applicant is requesting a Only 18-month is granted.

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

The recommended dose of CIALIS is 20 mg and is taken orally prior to anticipated sexual activity without regard to food. The maximum recommended dosing frequency is once per day.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable from Chemistry, Manufacturing and Control standpoint. This recommendation is based upon several issues identified during the review. The level of impurities, both in the drug substance and in the drug product were rather generous, therefore needs to be revised to reflect the actual manufacturing capability and stability characteristics of the product. Similarly, adequate information on the drug
substance reference standards is not provided and must be addressed to guarantee the highest purity of the drug substance. The system suitability of the analytical methods, which establishes the performance of the chromatographic method (HPLC) for meaningful interpretation of the drug substance specifications, needs to be provided. Sponsor must provide the required results (for maintaining the quality) on the which stored the drug substance.
The post approval stability commitment needs to be revised to control the quality of the future drug product batches.
Lastly, the final recommendation from the Office of Compliance for Eli Lilly sites (Drug product and Drug substance manufacturing sites) is still pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/RAgarwal/ MRhee/ D Spell Le-Sane/ Date: 26-FEB-2002

C. CC Block

HFD-820/EDuffy/Duu Gong Wu
52 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rajiv Agarwal
2/27/02 09:06:47 AM
CHEMIST

Moo-Jhong Rhee
2/27/02 09:44:53 AM
CHEMIST
I concur
# APPENDIX-I

### Establishments Evaluation Request

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<td>TABLETS</td>
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**Application Comment:** THIS IS AN API COMPOUND WHICH WILL BE FORMULATED INTO A 20 MG STRENGTH TABLET. (on 22-AUG-2001 by D. LIN (HYD-830) 301-827-4203)

**FDA Contacts:**
- R. AGARWAL, Review Chemist (HYD-580) 301-827-4237
- M. RAEZ, Team Leader

**Overall Recommendation:**
- ACCEPTABLE on 13-MAY-2003 by S. ADAMS (HYD-322) 301-827-9051
- WITHHOLD on 25-MAY-2003 by J. D. AMBROGIO (HYD-322) 301-827-9049
- WITHHOLD on 27-JUN-2002 by J. D. AMBROGIO (HYD-322) 301-827-9049
- WITHHOLD on 29-APR-2002 by J. D. AMBROGIO (HYD-322) 301-827-9049

**Establishment:**
- CPW 1813692
- FEI 1813692

**DWF No:**
- ELI LILLY CO/TIPPECANOE BOX 685 LILLY RD
- LAFAYETTE, IN 47902

**Responsibilities:**
- D.R. SUBSTANCE MANUFACTURER
- D.R. SUBSTANCE OTHER TESTER
- D.R. SUBSTANCE STABILITY TESTER

**Profile:**
- CSW
- GAI Status: NONE

**Establishment Comment:** DRUG SUBSTANCE MANUFACTURER. (on 22-SEP-2001 by D. LIN (HYD-830) 301-827-4203)

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This was a drug pre-approval, follow-up and cGMP inspection of a large API manufacturer.
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BIN 4/1-18/02 WILL BE CLASSIFIED VAI.
OC RECOMMENDATION 29-APR-2002
DO RECOMMENDATION 28-MAY-2002

RE 4-3-18/02 WAS CLASSIFIED VAI.
OC RECOMMENDATION 28-MAY-2002
SUBMITTED TO OC 11-JUN-2003
OC RECOMMENDATION 11-JUN-2003

Establishment: CPM 2619243
ELI LILLY INDUSTRIES INC
12.6 KM 65TH INFANTRY RD
CAROLINA, PR 00985

Page 29 of 31
### Establishment Evaluation Request

**DEPARTMENT:** FDA CDER EES  
**DATE:** 18-NOV-2003  
**PAGE:** 3 of 4

#### DMF No:

**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  

**Profile:** TOM  
**OAI Status:** NONE

#### Establishment Comment:
TADALAFIL TABLETS WILL BE MANUFACTURED AT THIS ALTERNATE FACILITY. THIS FACILITY ALSO PERFORMS THE PACKAGING, LABELING AND CONTROL TESTING OF THE FINISHED PRODUCT. (on 11-JUN-2003 by R. ADAMAL [1])

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