

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-368

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

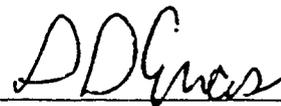
ITEM 13: PATENT INFORMATION**NDA 21368
Cialis™
(tadalafil)**

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of tadalafil, as indicated. This product is the subject of this application for which approval is being sought:

Patent Number	Patent Expiry Date	Type of Patent (Drug Substance, Drug Product, or Method of Use)
5,859,006	January 12, 2016	Compound
6,140,329	July 11, 2016	Method of use

The above patents are all owned by or exclusively licensed by Lilly ICOS LLC, Wilmington, Delaware.

Lilly Research Laboratories on behalf of Lilly ICOS LLC



Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

Date: June 7, 2001

ITEM 14: PATENT CERTIFICATION

**NDA 21368
Cialis™
(tadalafil)**

Lilly ICOS LLC (Lilly ICOS) claims a five year period of exclusivity for the use of tadalafil as provided by 21 C.F.R. 314.108(b)(2). As evidenced by the absence in the Orange Book that tadalafil has previously been approved by the FDA, to the best of Applicant's knowledge and belief, tadalafil has not previously been approved under section 505(b) of the FFDCA. Accordingly, Lilly ICOS submits tadalafil is a new chemical entity entitled to a five year period of exclusivity as provided by FFDCA 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii)(21 U.S.C. 355(c)(3)(D)(ii) and 355(j)(4)(D)(ii)).

Lilly Research Laboratories on behalf of Lilly ICOS LLC



g.t. _____
Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

Date: June 7, 2001

EXCLUSIVITY SUMMARY for NDA # 21-368

Trade Name Cialis™ Generic Name tadalafil

Applicant Name Lilly ICOS _____ HFD- 580

Approval Date November 21, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES/ x / NO / ___ /
- b) Is it an effectiveness supplement? YES / ___ / NO / x /

If yes, what type (SE1, SE2, etc.)?

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / x / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__/ NO /_x_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /__/ NO /_x_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /_x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_x_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Eufrecina DeGuia
Signature of Preparer

November 25, 2003
Date

Title: Regulatory Health Project Manager

(See appended electronic signature page)

Daniel Shames, M.D.
Signature of Division Director

November 25, 2003
Date

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Daniel A. Shames
11/21/03 10:10:22 AM

Debarment Certification

NDA Application No. 21368

Drug Name: Cialis™ (tadalafil)

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Lilly ICOS LLC, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

Lilly Research Laboratories on behalf of Lilly ICOS LLC



Gregory T. Brophy, Ph.D. Director
U.S. Regulatory Affairs

1 June 2001

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA#: 21-368 _____ Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: May 28, 2003 (Resubmission) Action Date: November 21, 2003

HFD 580 Trade and generic names/dosage form: Cialis (tadalafil)

Applicant: Lilly ICOS Therapeutic Class: 1S

Indication(s) previously approved: treatment of erectile dysfunction

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of erectile dysfunction

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Eufrecina DeGuia

Regulatory Health Project Manager

cc: NDA

HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

NDA ##-###

Page 3

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Jennifer L. Mercier
11/21/03 11:59:38 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-368	Efficacy Supplement Type SE-	Supplement Number
Drug: Cialis (tadalafil) tablets		Applicant: Lilly ICOS
RPM: Eufrecina DeGuia	HFD- 580	Phone # (301) 827-4260
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		1
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		November 21, 2003
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other N/A
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
General Information	
❖ Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE 4-29-2002
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release (X) Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	Included in Discipline's Reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X (See Meeting Minutes)
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	No meeting held
• Pre-NDA meeting (indicate date)	X
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X (Medical Team Leader)
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	November 21, 2003
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	MO Review (11-21-03)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	7-9-2002 (final)
❖ Biopharmaceutical review(s) (indicate date for each review)	11-19-03
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	completed
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	11-20-03
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See Chemist's Review
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	11-12-03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	Final
❖ CAC/ECAC report	Final

**This is a representation of an electronic record that was signed electronically and
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/s/

Jennifer L. Mercier
11/21/03 10:35:12 AM

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
ODE 3

Division of Reproductive and Urologic Drug Products

Date: November 21, 2003

From: Ashok Batra, M.D., Medical Officer, HFD-580

To: Mark S. Hirsch, M.D., Medical Team Leader, HFD-580

Subject: NDA 21-368, LillyICOS LLC
Cialis™ (tadalafil) for treatment of erectile dysfunction

1. Executive summary

The purpose of this memo is to provide the Medical Team Leader with my recommendation regarding regulatory action on NDA 21-368 following the sponsor's (LillyICOS) complete response to the FDA's approvable letter of April 29th, 2002. At this time, I recommend that this application should be approved.

At the conclusion of the original NDA review, there were five major issues (4 clinical and 1 chemistry) along with additional minor clinical and clinical pharmacology issues. The four major clinical issues were as follows:

1. Cialis-Nitrate interaction required further exploration to improve the safety of the population at risk of Cialis-Nitrate co-administration.
2. Cialis – Alcohol interaction needed further study.
3. The potential for Cialis potential to cause arrhythmias (through QT prolongation) needed to be explored.
4. Finally, the association of myalgia-back pain required more studies and analysis.

In my view the sponsor has resolved the clinical issues outlined in the approvable letter issued on April 29th, 2002. I believe the starting dose for the population with advanced renal impairment and the general population should be 5 mg and 10 mg, respectively. Secondly, dose adjustment to 10mg every 72 hours is required when Cialis is co-administered with certain drugs such as ketoconazole or HIV protease inhibitors. At this time, I believe the label that has been generated for Cialis™ will allow it to be marketed with adequate safety and efficacy.

2. Background

Erectile dysfunction (ED) is a multifactorial disease caused by atherosclerosis, diabetes, renal insufficiency, heart disease, smoking, alcohol use, other endocrinopathies, traumatic injury, neurologic dysfunction, psychological disturbances and certain concomitant medications. Over the last few years, there has been a considerable understanding of pharmacologic modalities to treat the ED patients.

Cialis (tadalafil) is a Type 5 PDE inhibitor. It was developed by the Lilly-ICOS Corporation because of its potential to improve upon Viagra. It has a prolonged half-life (17.5 hours) and therefore may allow for a longer period of responsiveness. The sponsor planned, designed and conducted an entire Phase 3 controlled and open-label, efficacy and safety development program outside of US (e.g. Canada, Taiwan, Australia, Europe, South America and Mexico). The NDA 21-368 was submitted on June 26, 2001. While Cialis was found to be effective, there were several medically significant issues that were not explored for safety. The sponsor was issued an approvable letter on April 29th, 2002.

It outlined several clinical issues that required resolution. These issues are described in the clinical review section below.

3. Clinical Review:

The Complete Response to the FDA's approvable letter for tadalafil dated April 29th, 2002, was submitted by Lilly ICOS LLC on May 27th, 2003. In this submission, the sponsor has addressed the issues outlined in the approvable letter. In addition, the sponsor submitted a report on the positive control study to assess the effects of tadalafil on the QT interval. The primary focus of this reviewer was on the sponsor's complete response to the issues stated in the approvable letter. The new safety data was also reviewed. The reviews from the contributing reviewers are also incorporated. The contributing reviewers included: Dr Handelsman: (Nitrate interaction, Alcohol interaction, Cardiovascular events and Backpain-Myalgia), Drs. Kenna and Jarugula (Clinical pharmacology, Drug-Drug interactions, QTc – effect). Drs. Norman Stockbridge and Wiley Chambers provided consultation on cardiac and ophthalmologic issues, respectively. The Office of Drug Safety also provided consultation regarding risk management and risk communication.

3.1. Nitrate Interaction:

The Clinical Deficiency #1 in the approvable letter states:

“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 20 mg for a period of time after Cialis dosing until no blood pressure interaction is seen.”

Sponsor's Response

The sponsor conducted a study (LVDN) to clearly define the duration of Cialis-nitrate interaction and submitted a Risk Management Program that describes plans for patient, pharmacist, and physician education regarding the nitrate contraindication and nitrate interaction with Cialis. A consult was requested from the Office of Drug Safety (ODS) regarding the Risk Management Plan (RMP). The primary reviewer of the nitrate interaction study was Dr Harry Handelsman.

3.1.1. Clinical Review Study LVDN

The sponsor's proposed protocol (LVDN) to address this issue was approved by the Division at the time of the 6/3/02 guidance meeting the sponsor. For this issue, the following materials were reviewed:

1. Review of Clinical Study LVDN--Complete Response, May 27, 2003.
2. Medical Team Leader's Memo recommending non-approval, April 26, 2002.
3. Approvable letter to sponsor, April 29, 2002.
4. Minutes of the June 3, 2002 Guidance Meeting.
5. Sponsor's Briefing Document, Type A Meeting June 3, 2002.

Study LVDN was a randomized, placebo-controlled, double-blind, two-period, crossover study of 166 subjects (including 32 diabetic and elderly, 46 were >60years of age). In each period, 20 mg tadalafil or placebo was dosed daily for 7 days. On Day 7, subjects received a final dose of tadalafil or placebo in the morning and 0.4 mg sublingual nitroglycerin (SL-NTG) at 2, 4, 8, 24, 48, 72, and 96 hours after tadalafil or placebo.

The interaction was studied by comparing the percentage of subjects with significant blood pressure changes in both the standing and supine positions after each nitrate administration. Clinically significant blood pressure changes were defined as:

1. Systolic blood pressure (SBP) < 85 mm Hg
2. Diastolic blood pressure (DBP) < 45 mm Hg
3. Decrease in SBP > 30 mm Hg
4. Decrease in DBP > 20 mm Hg.

The mean maximal blood pressure decreases (both standing and supine) following tadalafil or placebo were also assessed.

3.1.2. Clinical Study Results:

PD Results from LVDN: The primary pharmacodynamic endpoints were the mean maximal decrease in standing and supine systolic and diastolic BP after administration of NTG 0.4 mg in patients taking Cialis 20 mg daily for 7 days. As seen in the following tables, the hypotensive effects of NTG were augmented by co-administration of Cialis, but not by placebo, for 24 hours following the Cialis dose. At 48 hours post-Cialis and beyond, there were no differences in the hypotensive response to NTG in any population studied, including diabetics or the elderly.

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Table 1. Percentage of Subjects Experiencing Clinically Significant Blood Pressure Findings (IC351/Placebo) and Associated Statistical Analysis for the Overall Population

Criterion	Nitroglycerin dose (hr)						
	2	4	8	24	48	72	96
Primary endpoint:							
Standing systolic BP <85 mmHg	NP*	46/31 [<0.001]	31/21 [0.00754]	41/32 [0.0283]	28/27 [0.754]	23/28 [0.210]	27/25 [0.687]
Secondary endpoints:							
Standing diastolic BP <45 mmHg	NP*	19/6 [<0.001]	12/5 [0.0176]	16/8 [0.0101]	11/13 [0.581]	8/10 [0.582]	6/7 [0.807]
Decrease in standing systolic BP >30 mmHg	NP*	25/22 [0.423]	30/17 [0.00204]	48/33 [0.00197]	35/29 [0.133]	36/32 [0.338]	33/30 [0.416]
Decrease in standing diastolic BP >20 mmHg	NP*	15/10 [0.126]	18/13 [0.158]	31/20 [0.00957]	26/22 [0.263]	22/22 [0.891]	18/17 [0.766]
Supine systolic BP <85 mmHg	12/5 [0.0201]	12/4 [0.00504]	7/2 [0.0156]	8/3 [0.0117]	3/3 [0.700]	3/2 [0.560]	3/2 [0.651]
Supine diastolic BP <45 mmHg	4/1 [0.117]	5/4 [0.503]	4/1 [0.0540]	2/2 [0.837]	2/1 [0.177]	1/2 [0.184]	1/1 [0.996]
Decrease in supine systolic BP >30 mmHg	8/4 [0.0742]	3/2 [0.646]	4/2 [0.320]	10/3 [0.0161]	6/8 [0.628]	3/7 [0.0657]	8/4 [0.126]
Decrease in supine diastolic BP >20 mmHg	8/3 [0.0166]	3/1 [0.136]	5/1 [0.0467]	6/1 [0.0493]	3/2 [0.700]	3/6 [0.190]	1/3 [0.215]

*NP=Not performed; standing vital signs not taken until 3.5 hrs after tadalafil/placebo dose

Source: LVDN Section 14.2.3 (Table 1.1)

Reviewer's Comment: The hypotensive interaction between Cialis and NTG persists at least up to 24 hours, and is dissipated by 48 hours. The compensatory increases in standing and supine heart rate (as documented in the sponsor's Clinical Study LVDN, Main Report) up to 24 hours after Cialis or placebo in response to NTG were considered not to be clinically important. Other than non-statistically significant differences between tadalafil and placebo in decrease in standing systolic BP >30mmHg and decrease in standing diastolic BP >20 mmHg, there were no differences in any endpoint at or beyond 48 hours.

3.1.3. Adverse Events from LVDN:

For the overall population, the number of AE's was approx. 2-fold higher when NTG was administered in the presence of Cialis versus placebo. The AE profile was essentially the same as that previously reported in other studies. There were no deaths, and the single serious AE (sinus arrest) occurred in a subject approximately 8 minutes after receiving the 24 h NTG dose in the presence of placebo (not tadalafil). Telemetry review confirmed that this event lasted at least 13 seconds, after which the subject spontaneously reverted to sinus rhythm which persisted for an additional 3 hours of intensive monitoring in both the supine and standing positions. The subject was withdrawn from study.

Two subjects experienced single episodes of orthostatic hypotension following NTG in the presence of Cialis. These episodes were short-lived and resolved without sequelae.

Two subjects experienced asymptomatic ventricular extrasystoles 2 days after receiving the final dose of Cialis on Day 7 and were withdrawn from study. An additional subject experienced asymptomatic second degree AV block 2 days after the final Cialis dose. This resolved after 1 minute, and the subject was withdrawn from study.

Reviewer's Comment: Although the Cialis/nitrate interaction is the primary focus of this review, it is of interest that the percentage of subjects reporting back pain and myalgia in this trial was approximately 30-50% in each population studied (tadalafil and placebo).

3.1.4. Summary of Clinical Findings (LVDN):

1. For the population studied (including diabetics and the elderly) the hypotensive effects of NTG was augmented in the presence of Cialis for the first 24 hours. At or beyond 48 hours following Cialis or placebo, there was no difference in the hypotensive response to NTG.
2. There were non-statistically significant differences in two secondary endpoints at 48 hours: decrease in standing systolic >30 mm Hg and decrease in standing diastolic < 20 mmHg.

3. There were no clinically significant changes in the compensatory increases in heart rate in response to NTG-induced hypotension irrespective of time NTG was given after Cialis or placebo.
4. There were no serious AEs related to Cialis, either alone or when combined with NTG.

3.1.5. Conclusions, Recommendation, Labeling:

Sponsor's conclusions

1. The administration of short acting nitrates is contraindicated for at least 24 hours after the administration of Cialis.
2. Short-acting nitrates may be safely administered at or beyond 48 hours after the last dose of Cialis.

Reviewer's conclusions

Because there is no data for the period between 24 and 48 hours, this reviewer takes the position that only at 48 hours is there no augmentation of the hypotensive response to nitroglycerin by tadalafil. Nevertheless, in large part, the reviewer agrees with the sponsor's conclusions.

Of note, there are still non-statistically significant differences between tadalafil and placebo in two secondary endpoints at 48 hours: decrease in standing systolic >30 mm Hg and decrease in standing diastolic < 20 mmHg. While these are not "hypotensive responses" by the per-protocol definition, nor by reasonable clinical criteria, they may reflect a minor vasodilatory interaction of tadalafil and placebo even at 48 hours.

Recommendations

It is recommended that the Division accept the conclusion that the available evidence supports the claim that there is *no significant pharmacodynamic interaction* between

Cialis and short-acting nitrates at or beyond 48 hours following a dose of Cialis, especially with regards to adverse effects on BP.

Therefore, the label should state that nitroglycerin is contraindicated in toto; with evidence of hypotensive interaction occurring for up to 48 hours after a Cialis dose. Even at or beyond 48 hours, patients should be in a monitored setting if nitroglycerin is required.

Labeling

The label should specifically state that short-acting nitrates are contraindicated up to 48 hours following a dose of Cialis. Even at 48 hours such use should be limited to the monitored setting and only when deemed medically necessary.

Sponsor's Proposed Risk-Management Program (RMP):

The sponsor submitted a Risk Management Program with the primary goal of reducing the risk of concomitant use of nitrates and tadalafil. The plan included the use of patient, pharmacist, and physician education regarding the nitrate contraindication and nitrate interaction.

It also includes special education for emergency health care professionals likely to see patients with chest pain (for example, emergency physicians, emergency nurses, and emergency medical technicians). Patients will be educated through the use of a patient package insert (PPI), through information provided in patient brochures, and in direct to consumer provision of information. The sponsor submitted a plan for assessment of the Risk Management Program. The team from Division of Drug Risk Evaluation in Office of Drug Safety reviewed the proposed Risk Management Plan and provided comments.

Reviewer's Comments:

1. Patients should be given instructions for safe use through the patient package insert. Sponsor has agreed to the Division's recommendations for the PPI.
2. Detailed instructions should be given to emergency health care professionals through educational materials. Sponsor has agreed to distribute such

[Redacted]

Overall assessment of the response (NTG issue):

1. The sponsor has adequately explored the issue of Cialis–Nitrate co-administration. In study LVDN, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between Cialis and NTG was not observed.
2. The label should include the following:

- [Redacted]
- [Redacted]
- [Redacted]

3.2. Cialis–Alcohol Interaction:

Clinical Deficiency #2 in the approvable letter states :

“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 10 mg study differ from the 20 mg Cialis study with respect to clinically significant changes in blood pressure.”

Regulatory History: Based upon a large, well-controlled, and adequate drug-alcohol interaction study at 20mg that revealed no interaction, but findings of some degree of interaction in a 10mg study, Study LVET was proposed by sponsor. On 13 December 2002, the final protocol for Study LVET was reviewed and found acceptable by the clinical pharmacology reviewer, Dr Jarugula.

Sponsor's Response

The sponsor submitted the results of Study LVET. This was a randomized, double-blind, placebo-controlled, three-way crossover study assessing the effects of 20 mg tadalafil co-administered with 0.7 g/kg ethanol after an extended fast, versus either agent alone. Fifty-five subjects entered the study and 53 completed the study. Supine and standing blood pressures and heart rates were measured at 17 time points during the first 12 hours after tadalafil or placebo administration and again at 24 hours. Additionally, blood was drawn to assess pharmacokinetic parameters for tadalafil and ethanol. The primary reviewer of the Study Report for LVET was Dr. Harry Handelsman.

3.2.1. Clinical Review

The following materials were reviewed:

1. Review of Clinical Study LVET--Complete Response, May 27, 2003.
2. Medical Team Leader's Memo recommending non-approval, April 26, 2002.
3. Clinical Pharmacologist's (S. Roy) original Cialis NDA review including reviews of Study LVAE and LVDO.
4. Amendment to NDA Dated October 13, 2003 including Executive Summary of Study LVFS.
5. Approvable letter to sponsor, April 29, 2002.
6. Clin-pharm reviews of protocol LVET, May 20 and November 8, 2002.
7. Minutes of the June 3, 2002 Guidance Meeting.
8. Sponsor's Briefing Document, Type A Meeting June 3, 2002.

3.2.2. Clinical Results for Study LVET

PK Results: As shown in the tables below, there were no significant pharmacokinetic differences for tadalafil between the combination group and the Cialis + placebo alcohol group.

Table 2. Geometric Mean (CV%) PK Parameters for tadalafil

Parameter	Cialis 20mg & alcohol 0.7mg/kg (n=54)	Cialis 20mg & alcohol placebo (n=54)
AUC (0-tlast)	5107 µg.h/L (23.2)	5157 µg.h/L (29.2)
AUC (0-24)	5092 µg.h/L (23.2)	5143 µg.h/L (29.2)
Cmax (µg/L)	349 (25.8)	356 (29.4)
Tmax (median, hrs)	3.09 (1.00-4.12)	1.94 (1.08-4.13)

Source: LVET Section 14.2.2. (Table 1)

Table 3. Geometric Mean (CV%) PK Parameters of alcohol

Parameter	Cialis 20 mg & alcohol 0.7 mg/kg (n=53)	Cialis placebo & alcohol 0.7 mg/kg (n=51)
AUC (0-tlast)	131 mg.h/dL (12.8)	126 mg.h/dL (13.9)
AUC (0-2)	127 mg.h/dL (12.2)	121 mg.h/dL (14.4)
Cmax (mg/dL)	84 (15)	81 (15)
Tmax (median, hrs)	0.83 (0.33-1.60)	0.83 (0.25-1.58)

Source: LVET Section 14.2.2. (Table 1)

Reviewer's Comment: Mean blood alcohol concentration-time profiles were also similar following co-administration of alcohol with Cialis and with placebo.

PD Results: The primary pharmacodynamic endpoint was the maximum reduction from baseline in mean standing systolic BP. As seen in the following two tables, there were no statistically significant differences between the combination group and either alcohol alone or Cialis alone in the primary endpoint: maximum reduction from baseline in *mean* standing systolic BP.

Table 4: Study LVET Pharmacodynamic Results; Combination Group Versus Cialis-placebo + alcohol, presented as group mean values.

Parameter	Cialis 20 mg & alcohol 0.7 g/kg (n=55)	Cialis-placebo & alcohol 0.7 g/kg (n=55)	Mean difference (Cialis & alcohol vs. Cialis-placebo & alcohol)
Primary endpoint:			
Max. decrease in standing systolic BP (mmHg)	17.0	15.3	1.73
Secondary endpoints:			
Max. decrease in supine systolic BP (mm Hg)	14.5	14.8	-0.333
Max. decrease in supine diastolic BP (mm Hg)	12.9	11.5	1.40
Max. decrease in standing diastolic BP (mm Hg)	14.9	13.5	1.42
Max. increase in supine heart rate (bpm)	24.3	21.3	2.98
Max. increase in standing heart rate (bpm)	32.1	29.3	2.89

Source: LVET Section 14.2.3. (Table 1.1)

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Table 5: Study LVET Pharmacodynamic Results; Combination Group Versus Cialis + alcohol-placebo, presented as group mean values

Parameter	Cialis 20 mg & alcohol 0.7 g/kg (n=55)	Cialis 20mg & Alcohol-placebo (n=55)	Mean difference (Cialis & alcohol vs. Cialis & alcohol-placebo)
Primary endpoint: Max. decrease in standing systolic BP (mmHg)	17.0	13.7	3.29
Secondary endpoints: Max. decrease in supine systolic BP (mm Hg)	14.5	11.6	2.86
Max. decrease in supine diastolic BP (mm Hg)	12.9	12.2	0.668
Max. decrease in standing diastolic BP (mm Hg)	14.9	13.5	1.44
Max. increase in supine heart rate (bpm)	24.3	16.4	7.92
Max. increase in standing heart rate (bpm)	32.1	19.8	12.4

Source: LVET Section 14.2.3. (Table 1.2)

An outlier analysis was conducted using a variety of endpoints that may be considered “clinically significant”. While there were no statistically significant differences in the analysis of mean changes from baseline, the outlier analysis demonstrated that more patients experienced clinically significant changes in BP on the combination of tadalafil and ethanol than on either alone.

In order to determine whether the findings of the outlier analysis resulted in medically significant adverse events, the reported adverse events were analyzed in detail (see Tables 6 and 7 below).

Table 6: Study LVET; Summary of Adverse Events

Treatment	No. Subjects	Subjects (%) with AE's	Number of AE's and severity	Subjects (%) with drug-related AE's	Number of drug-related AE's and severity
Cialis 20mg & alc. 0.7 g/kg	54	37 (68.5)	Mild 34 Moderate 45 Severe 0	22 (40.7)	Mild 9 Moderate 23 Severe 0
Cialis-placebo & alc. 0.7 g/kg	53	18 (34)	Mild 18 Moderate 10 Severe 0	4 (7.5)	Mild 2 Moderate 3 Severe 0
Cilais 20mg & alc.-placebo	54	15 (27.8)	Mild 19 Moderate 11 Severe 0	9 (16.7)	Mild 10 Moderate 6 Severe 0

Source: LVET Section 14.3.4. (Table 1)

Reviewer's Comment: About one third of patients report adverse events in the alcohol-only period.

The frequency of treatment-emergent AE's by type is seen in the following table:

Table 7: Study LVET; Number of Subjects with AE's

Adverse Event	Cialis 20 mg & Alcohol 0.7 g/kg (N=54)	Cialis-placebo & alcohol 0.7 g/kg (N=53)	Cialis 20 mg & alcohol-placebo (N=54)
Headache	16	3	5
Dizziness	12	2	3
Feeling drunk	3	4	0
Orthostatic hypotension	3	0	0
Spontaneous erection	2	1	1
Fatigue	3	0	1
Flushing	4	0	0
Nausea	3	1	0
Myalgia	2	0	2

Reviewer's Comments:

1. The most commonly reported adverse events were headache and dizziness with the incidence of these being highest following co-administration of Cialis with alcohol.
2. The term dizziness refers to symptoms *without* documented significant reductions in blood pressure; only those 3 events coded as orthostatic hypotension were associated with documented significant reductions in blood pressure.
3. No treatment, other than postural alteration, was required for the 3 patients with orthostatic hypotension.

4. In all 3 patients who reported orthostatic hypotension (Subjects #5, #13 and #51), the event occurred following dosing with Cialis but *prior* to the intake of alcohol. In Subject #5, dizziness was reported again at 4 hours after dosing with alcohol but at that time, standing vital signs were not measured.

5. Of those patients in whom standing vital signs were not measured during an episode of dizziness, all available data was carefully examined. Using a conservative analysis, data suggests that a total of seven patients in the combination period may have had orthostasis compared with 5 patients in the Cialis-alone arm and 1 patient in the alcohol-alone arm. Therefore, even using a conservative analysis for missing data, the incidences of orthostasis were only slightly worse for combination relative to either agent alone.

3.2.4. Summary of Sponsor's Conclusions Regarding LVET:

1. There were no statistically significant differences between Cialis + alcohol versus alcohol alone or Cialis alone in the following endpoints:
 - mean maximal decrease in standing or supine systolic blood pressure.
 - mean maximal decrease in standing or supine diastolic blood pressure.
 - mean maximal increase in supine or standing heart rate.
2. The mean maximal decrease in supine systolic blood pressure was actually greater for alcohol alone than for Cialis alone.
3. Plasma concentration vs time profiles for tadalafil were similar following co-administration of alcohol or alcohol placebo.
4. Blood concentration vs time profiles of alcohol (up to 2 hours post dose) were similar following co-administration of Cialis or placebo.
5. Co-administration of Cialis and alcohol were "reasonably well tolerated", although the incidence of adverse events was highest in the combination group.
6. The number of treatment-emergent episodes of orthostatic hypotension (n=3) were comparable to that following Cialis alone, and two of those three patients reported orthostatic hypotension only prior to alcohol intake.

3.2.4. Reviewer's Conclusions (LVET)

Reviewer's Conclusions:

1. Analysis of mean parameters of blood pressure and vital signs do not reveal a clinically significant interaction between Cialis and alcohol 0.7 gm/kg. However, the outlier analysis demonstrates a difference between groups.
2. Analysis of clinical adverse events reveals an increased incidence of headache and dizziness in the combination group, but, in general, significant reductions in BP were not seen in those patients who reported headache or dizziness.
3. The number of treatment-emergent episodes of orthostatic hypotension after Cialis & alcohol was comparable to that seen with Cialis-alone. In all 3 patients, who reported orthostatic hypotension, that event occurred prior to alcohol intake.
4. Co-administration of Cialis and alcohol was generally well tolerated, although the incidence of overall AE's (especially headache and dizziness) was higher than that seen in the alcohol-alone or Cialis-alone groups.

3.2.5. Study LVFS

On October 13, 2003, sponsor submitted results from a fourth alcohol interaction study, Study LVFS. This study was similar in design to LVET and previous Studies LVDO and LVAE. It was randomized, placebo- and active-controlled, blinded, three period crossover trial. Patients received each of the following three treatment: Cialis 20mg (or active comparator) & 0.7 gm/kg alcohol, Cialis (or active comparator)-placebo & 0.7 gm/kg alcohol, and Cialis 20mg & alcohol-placebo. Treatment periods were separated by 7-day washouts. In order to allow for the investigation of the active comparator, this study was conducted in two identical parts, the only difference being use of Cialis in one part (Part A) and active comparator in the other (Part B). Alcohol was taken at the time of known maximum plasma concentration of both drugs. Thirty-six patients were enrolled and completed both parts.

The major difference of this study compared with previous studies was the issue of fasting and hydration. Sponsor believed that fasting and dehydration may have led to some of the blood pressure changes seen in LVET. In designing this trial (LVFS), the procedures included providing a light lunch approximately 1 hour after the alcohol dose and an afternoon snack (rather than a large lunch at 2 hours after alcohol intake) and

providing water ad lib until one hour after alcohol intake. In addition, there was a single blood draw for analysis of blood alcohol levels, rather than multiple phlebotomies.

In this trial, the sponsor's presentation of the data reveals little evidence of a pharmacodynamic interaction between Cialis 20mg and alcohol, even at a dose of 0.7mg/kg.

For example, the mean maximal decrease from baseline in standing systolic BP was 14.4 mm Hg, 13.3 mm Hg, and 13.8 mm Hg for the combination group (Cialis & alcohol), alcohol-alone group, and Cialis-alone group, respectively. Mean differences between the combination group versus alcohol alone and Cialis-alone groups was 1.07 mm Hg, and 0.56 mm Hg, respectively. These differences were not statistically significant.

In an outlier analysis of "clinically meaningful changes" in vital signs, the difference between groups was small. There was a slightly greater number of patients in the combination group demonstrating these findings, as compared to alcohol alone or Cialis alone.

Finally, in terms of adverse events, there were few. These include two patients treated with combination reporting dizziness, versus one with alcohol alone. Orthostatic hypotension was not reported by any patient treated with Cialis, one alcohol alone and one with comparator alone.

In summary, the sponsor's presentation of results in LVFS do not reveal a worrisome interaction and this may be due in part to simply to changing the conditions of the trial by not enforcing a fast (e.g. allowing access to water, and providing an earlier lunch and an afternoon snack).

3.2.6. Overall Recommendation, Assessment Response and Labeling in Regard to Alcohol and Cialis:

Recommendation

It is recommended that the Division provide information in the label describing the results of the alcohol studies. Despite two trials revealing no interaction, it seems prudent to add cautionary wording to the label in regard to excessive alcohol use based upon the results of LVET.

In attempting to explain the differing outcomes of these trials, the fact that there was some interaction in both studies that used 0.7 gm/kg of alcohol may point to alcohol dose as a possible etiology. Alternatively, the lack of access to fluids and forced fasting may have enhanced vasodilatory adverse events and lowering of BP. This concept is supported by the results of Study LVFS.

Labeling:

Labeling should be revised to present the results of these alcohol interaction studies along with a Precaution in the Information to Patients section and the PPI to avoid excessive alcohol use (e.g. 5 units or greater) while taking Cialis.

Overall assessment:

The sponsor has adequately explored the issue of Cialis –Alcohol co-administration.

The label should be amended to reflect that:

1. Alcohol and CIALIS, a PDE 5 inhibitor, act as mild vasodilators.
2. Substantial consumption of alcohol (e.g. 5 units or greater) in combination with CIALIS, can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness and headache.

3.3. Effects of Tadalafil on Ventricular Repolarization

Clinical Deficiency #3 in the approvable letter States:

“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 80 mg 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.”

Regulatory History:

03 June 2002, the sponsor submitted a retrospective QTc Analysis Plan that described the analysis of the ECG data to be conducted.

On 12 September 2002, the sponsor submitted the results of Studies LVBG, LVBS, and LVBU for review. This retrospective analysis was found not to be sufficient to address this deficiency. The sponsor was advised to conduct a positive control study.

On 4 March 2003, DRUDP communicated to the sponsor that the results of the positive control QTc study (LVFB) are needed to address Clinical Deficiency #3 in the approvable letter.

Sponsor's Response:

Study LVFB, a randomized, placebo and active-control study carries the burden to assess the electrophysiologic effect of 100 mg IC351. Drs. Stockbridge and Kenna contributed to the review of this part of the Complete Response.

3.3.1. Study LVFB:

This was a randomized, double-blind, placebo-controlled study to assess the electrophysiologic effect of 100 mg IC351 or placebo on QT Interval. Ibutilide was used as an open-label positive control. The study was conducted in healthy males.

The primary objective of the study was to demonstrate that IC351 had no adverse effect on ventricular repolarization as assessed by QTc when given as a 100 mg single dose. Results were measured for a statistically significant difference between: 1) ibutilide and placebo, 2) ibutilide and tadalafil, and for 3) statistical equivalence of IC351 and placebo. Ninety-five males, aged between 18 and 65 years entered the study and 90 completed the study. On Day 1 of each treatment period, single oral doses of Cialis or placebo, or a 10-minute intravenous infusion of ibutilide (for a subset of subjects). There was a washout of at least 12 days between treatment periods. A post-study assessment was performed within 7 days of the last dose of study drug.

3.3.2. LVFB Results:

The sponsor used several methods to correct QT interval for heart rate. For an ANOVA model fitting RR as a covariate, mean changes in QTc interval for tadalafil versus placebo was 3.3 milliseconds with two-sided 90% CI of (1.7, 5.0). The difference in the mean change from baseline for tadalafil relative to placebo with respect to an individual correction method (“QTcI”), the Fridericia correction (“QTcF”), and the in-house “Lilly” correction (“QTcL”) was 2.8, 3.5 and 5.0 msec, respectively. The sponsor reported that QTcI and QTcF intervals were independent of heart rate while QTcL yielded a positive correlation with heart rate.

The following table shows the corrected QTc effect utilizing various methods of correction (see table below).

Table 8: Mean Change (90% CI) from Baseline to Tmax*

Comparison	Heart rate (bpm)	QT (ms)	QTc Model based (ms)	QTcI (Individual) (ms)	QTcF (Fridericia) (ms)	QTcL (Lilly) (ms)
100mg Cialis (relative to placebo)	3.1 (1.7,4.5)	-2.4 (-5.5,0.7)	3.3 (1.7,5.0)	2.8 (1.2,4.4)	3.5 (1.9, 5.1)	5.0 (3.3,6.7)
Ibutilide (relative to placebo)	1.8 (0.4,3.2)	5.7 (2.0,9.4)	9.6 (7.6,11.6)	8.9 (6.9,10.8)	9.5 (7.6,11.4)	10.4 (8.5,12.4)
Ibutilide vs Cialis	-2.3 (-3.8, -0.8)	10.9 (7.2,14.7)	6.8 (5.0,8.7)	6.9 (5.0,8.8)	7.1 (5.3, 8.9)	6.1 (4.3,7.8)

Source: LVFB 11.13; *Tmax for 100 mg Cialis and matched placebo, post-infusion (11 to 20 minutes) for Ibutilide

Reviewer's Comments :

1. This study showed equivalence between Cialis and the placebo in its effect on QTc with sufficient assay sensitivity.
2. This reviewer believes that Cialis demonstrated a clinically insignificant effect on QT prolongation in the study LVFB.
3. Dr Kenna, in her review, noted the following:
 - “Based on an analysis of a total of 8,011 individual ECG QTc measurements, in the tadalafil (IC351) period, 0.7% and 0.9% of the measurements of change in QTcI and QTcF, respectively, from baseline were greater than 30 msec. These outlying values were observed in 8.6% and 15.1% of subjects. The effect of tadalafil on QT interval was greater than that for placebo but less than that for ibutilide—2% and 2.6% of the measurements of change in QTcI and QTcF, respectively, from baseline were greater than 30 msec in the ibutilide period. These outlying values were observed in 13.4% and 16.4% of subjects. In the placebo period, 0.2% and 0.3% of the measurements of change in QTcI and QTcF, respectively, from baseline were greater than 30 msec and these outlying values were observed in 6.6% and 7.7% of subjects. No subject experienced a QTc change from baseline in the placebo, tadalafil and ibutilide periods greater than 60 msec. Approximately ten percent (10%) of the outlying.

values were >45 msec. No individual post-baseline QTc value exceeded 450 msec in the tadalafil and placebo periods.

- There is a small (3 to 5 msec increase), but, possibly, clinically insignificant effect of tadalafil on QT interval.
- The magnitude of prolongation should be reported in the labeling.”

Overall assessment of the response:

The sponsor has adequately explored the effects of tadalafil on ventricular repolarization. The label should include the following paragraph in the clinical pharmacology section:

“Effects of Cialis on Cardiac Electrophysiology: In a randomized, double-blinded, placebo and active (intravenous ibutalide)-controlled crossover study in 90 healthy males aged 18 to 53 years, single 100mg doses of Cialis had no clinically relevant effects on the corrected QT interval (QTc) when compared with placebo. The mean change from baseline in QTc in the placebo group and tadalafil 100mg group was 3.5 milliseconds and 6.9 milliseconds, respectively. The standard error for each group was 0.7 milliseconds. The difference between groups was 3.3 milliseconds (two sided 90% CI = 1.7, 5.0). Since the upper limit of the CI was below the pre-defined limit of 10 millisecond, tadalafil was declared non-inferior to placebo. In this study, the mean change from baseline in QTc following ibutalide administration was 12.7 milliseconds with a standard error of 0.8 milliseconds.”

3.4. Back Pain and Myalgia

Clinical Deficiency #4 in the approvable letter states:

“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.”

Regulatory History

On April 29, 2002, the Division requested that the sponsor provide an analysis of reports of the back pain/myalgias events and further prospective investigation. The Division requested medical work-up of subjects who had back pain or myalgia so as to rule out the presence of medically significant disease processes, including vasculitis, and other potential effects on the kidney (a "prospective algorithm"). The Division also requested that the sponsor submit plans for such a work-up to the Division for concurrence.

On June 3, 2002, the sponsor submitted a briefing document for a guidance meeting with the Division on June 3, 2002 which included the following points:

1. The reported back pain/myalgia AE's were generally mild or moderately severe.
2. At the time of the briefing, only 2/949 subjects (0.2%) in the phase-3 studies discontinued due to back pain or myalgia AE's.
3. There was no evidence of treatment-related pathology due to back pain/myalgia in studies with 6 months of daily dosing or over one year of intermittent dosing.
4. If a subject developed back pain/myalgia AE's, they tended to manifest early in the course of the study and in most cases, spontaneously resolved, without sequelae, despite continued dosing.
5. The back pain/myalgia AE's were noted more frequently in normal volunteers than in ED subjects.
6. The prevalence of back pain/myalgia AE's declined over time.
7. Some investigators noted that back pain tended to diminish during ambulation.
8. There was no apparent increase in incidence of back pain/myalgia AE's with age.

The Division's Guidance to sponsor at that time included the following points:

- The sponsor's analysis algorithm is acceptable.
- The sponsor's Complete Response must include algorithm results from approximately 50 subjects.
- Renal blood flow and MRI studies are deemed acceptable, and should be included in the Complete Response.

Sponsor's Response

The sponsor conducted a retrospective analysis of reports of adverse events of the back pain or myalgia in clinical trials and clinical pharmacology studies. The sponsor also prospectively evaluated all patients who reported back pain or myalgia in new studies to rule out medically significant disease processes. The sponsor also conducted a study to assess renal blood flow, potential inflammation, and blood pooling following single doses of tadalafil up to 80 mg. The primary review of this response was conducted by Dr Harry Handelsman.

3.4.1. Executive Summary/Back Pain and Myalgia (BPM):

It is recommended that the Division accept the conclusion that the available evidence supports the hypothesis that BPM associated with the use of Cilais does not reflect medically significant underlying pathology. In addition, it is recommended that the sponsor propose a lower than standard dose for patients with mild or moderate renal impairment, and indicate in the label that BPM may be severe in approximately 4% of patients and may require narcotic analgesia (e.g. codeine).

3.4.2. Summary of Clinical Findings

BPM was most often described as diffuse lower lumbar and/or bilateral gluteal pain, frequently exacerbated by recumbency and relieved by ambulation. The incidence of pooled BPM events ranged from 8.1% in placebo-controlled trials to 17.5% in the clin-pharm studies, with the majority being of mild or moderate in severity. These events were usually reported within 12-48 hours after dosing and spontaneously resolved without sequelae within 24 hours of onset and despite continued dosing. Although the severity of BPM was reported as severe in 4-5% of subjects it rarely led to discontinuation of drug or required use of narcotic analgesia. The prevalence of BPM tended to decline over time, despite continued exposure. No patient had a serious AE or required hospitalization.

Reviewer's comments:

1. This description suggests the absence of a serious underlying medical condition.
2. The sponsor contends that BPM appears to be a class effect of PDE-5 inhibitors.
3. The mechanism for back pain and myalgias remains conjectural. The sponsor has hypothesized that the pooling of venous blood in the large muscle groups of the gluteal and low back regions were causal reasons for BPM. Again, this is conjectural

Among patients presenting BPM (including those with renal disease), physical examinations, imaging, or laboratory testing failed to detect any significant abnormalities or pathology associated with these events.

3.4.3. Back Pain and Myalgia: Special Populations

Geriatric: There is no indication of an increased incidence of BPM noted in the elderly any study database.

Renal insufficiency: In subjects with ESRD undergoing dialysis, there were no reports of BPM. However, in subjects with moderate renal impairment (with drug exposure 2-3 fold higher than subjects without renal disease), BPM was reported after either the 5 or 10 mg doses of Cialis but the 10 mg dose was more poorly tolerated than the 5mg dose.

3.4.4. Description of Clinical Data and Sources for Back Pain/Myalgias Review

The following materials were reviewed:

1. Review of Back Pain and Myalgia Events and Prospective Laboratory Evaluation of Back Pain and Myalgia - Complete Response, May 27, 2003.
2. Clinical Study (LVFA) Main Report: Effects on Effective Renal Plasma Blood Flow and Lumbar and Gluteal Vasocongestion of 20 mg or 80 mg IC351.

3. Clinical Study (LVDT) Main Report. Investigating the Tolerability and Pharmacokinetics of IC351 in ESRD Subjects on Haemodialysis.
4. Tadalafil Safety Update Report, June 2, 2003.
5. Division's Clinical Pharmacology and Biopharmaceutics Review, April 29, 2002.
6. Minutes of the June 6, 2002 Guidance Meeting.

3.4.5. Clinical Review Methods

The clinical trials LVFA and LVDT were reviewed in detail. Other material noted above, including clinical pharmacology studies LVEV and LVAJ in the Complete Response were also reviewed in detail.

3.4.6. Clinical Results in Regard to Back Pain and Myalgias

In 50 clinical pharmacology studies, including a total of 2262 subjects, the incidence of BPM was 17.5%. This is compared to an overall incidence of 8.1% in all placebo-controlled studies (all doses). In clinical pharmacology studies, the incidence of BPM appears to be dose-related (Table 9).

Table 9: Incidence and Severity of BPM, Retrospective Analysis

Treatment Group	N	Incidence N (%)	Severity		
			Mild	Moderate	Severe
Placebo	569	21 (3.7)	11	9	1
Tadalafil 2.5mg	16	2 (12.5)	0	2	0
Tadalafil 5.0 mg	195	22 (11.3)	14	5	3
Tadalafil 10 mg	930	169 (18.2)	100	66	3
Tadalafil 20 mg	363	104 (28.7)	52	48	4
Tadalafil 40 mg	45	5 (11.1)	4	1	0
Tadalafil 50 mg	14	5 (35.7)	1	4	0
Tadalafil 100 mg	18	14 (77.8)	5	9	0

In the clinical pharmacology studies, 62.5% of subjects did not require treatment for BPM, and only 11/1502 subjects (0.7%) required narcotics. In all, 9 subjects discontinued study due to pain; four each at 10 and 20 mg, and 1 subject at the 50mg dose. This

database indicated no significant difference in the incidence of BPM among patients 60 years of age or older versus the overall treatment population.

In all the placebo-controlled studies the incidence of BPM was 8.1% for drug versus 3.7% for placebo, with no apparent dose-relatedness. Reported intensity of pain was severe in 4.1% of drug-treated subjects versus 5% in placebo, and 56.6% of subjects did not require any treatment.

BPM was most frequently reported within 12-48 hours after dosing, and rarely reported after 72 hours. Spontaneous resolution of BPM was seen within 48 hours of onset in 52-58% of subjects.

Reviewer's Comment: Resolution of BPM despite continued dosing suggests that these AE's are unlikely to be related to serious medical conditions.

The sponsor conducted a prospectively designed study (involving 142 subjects taking both single dose or 7 day multiple dosing) in order to establish a differential diagnosis of BPM within 48 hours of onset, including physical examinations and laboratory tests. None of this data (comparing baseline with 48-hour samples) identified any inflammatory conditions or immune disease-related abnormalities, and there was no differences between patients with or without symptoms.

In another study involving 483 ED patients, 3 groups of 161 subjects each were exposed to 10 or 20 mg of tadalafil or placebo. BPM was reported in 13 (8.1%), 15 (9.3%) and 2 (1.2%) of subjects respectively. Eleven of the 30 subjects who reported BPM among this group completed the algorithm for laboratory testing and demonstrated no clinically important changes.

In all studies, no subject reported a serious AE related to BPM, no subject required hospitalization for BPM, and discontinuation due to BPM was rare.

3.4.7. Prospective Studies in Regard to Back Pain/Myalgia

STUDY LVFA:

Study LVFA was designed to evaluate the effects of 20 or 80 mg of tadalafil vs placebo on renal blood flow and lumbar and venocongestion as measured by renal radionuclide scans, Gadolinium enhanced MRI, and FDG-PET in 20 healthy males.

In the 17 subjects who completed the study, there were no significant differences in effective renal blood flow and renal function between the 2 doses of active drug and placebo. There were no significant differences in standard uptake value (as indicator of tissue inflammation) in the lumbar and gluteal regions, as measured by FDG-PET, or changes identified by MRI, in subjects with or without reported BPM. No subject reported myalgia. Of the 2 subjects reporting back pain, it commenced at 17 hours in one subject after a 20 mg dose of drug and lasted 35 hours. In the other subject, it began 61 hours after an 80 mg dose and lasted 20.5 hours.

Reviewer's Comment: These radiographic techniques have been validated for identifying significant inflammatory processes, but may not be sufficiently sensitive to detect moderate changes in pooling of venous blood in the low back and gluteal regions.

In this study, in 17 subjects exposed to drug, 55.6% had mild to moderate AE's after 20mg, and 75% had drug-related AE's (including 1 severe) after 80 mg. The most frequently reported AE's were headache and back pain, with similar incidence using either dose. No serious AE's were reported. Three patients prematurely discontinued and of these, 2 subjects failed to return for all study procedures, and 1 signed a consent form but failed to return for any study procedures.

In studies LVCD (103 subjects, 10 mg) and LVCZ (111 subjects, 20 mg), BPM was seen in 11.7% and 4.5% at 3 and 6 months, and 16.2% and 6.6% at 3 and 6 months in the respective trials. No subjects discontinued because of pain.

In clinical pharmacology study LVEV, conducted in 8 healthy male volunteers, 20 mg of tadalafil was co-administered with 20mg ritonavir (which inhibits the metabolism of tadalafil to its major metabolite). Exposure to this metabolite (methylcatechol

glucuronide) was reduced 66% and its C_{max} was reduced 78%. Concentrations of tadalafil were maximized. In this study, BPM was reported in 3/8 subjects, an incidence comparable to that reported with tadalafil alone.

In clinical pharmacology study LVDT, investigating the pharmacokinetics of both tadalafil and its metabolite in 16 ESRD patients undergoing hemodialysis thrice weekly, it was found that, on average, the exposure to drug and metabolite was respectively 2.1-fold and 3.1-fold higher than in normal subjects. A total of 6, 12, and 6 subjects received a single dose of 5, 10, or 20 mg of drug respectively. Despite higher drug exposure than seen in healthy subjects, no subject reported BPM after 24 episodes of treatment.

Clinical pharmacology study LVAJ evaluated 5 and 10 mg doses of tadalafil in 28 subjects with mild or moderate renal impairment, defined as creatinine clearance of 51-80 and 31-50 mL/min. respectively. A single 5 or 10 mg dose of drug in the moderate renal impairment group resulted in an approximately 2-fold greater exposure to drug and a 2.2-2.6-fold greater exposure to metabolite than in healthy subjects. The T_{max} for the metabolite was 18 hours in healthy subjects, and 36 and 48 hours in subjects with mild and moderate renal impairment respectively. The 10 mg dose was poorly tolerated in subjects with moderate impairment (4/6 reported BPM) but the 5mg dose was well-tolerated. In this study, BPM was reported in 1/4 and 1/8 healthy subjects taking 5 or 10 mg respectively; and 1/3 and 0/5 subjects with mild impairment taking 5 or 10 mg respectively.

3.4.8. Conclusions, Recommendations, and Labeling

Conclusions

The sponsor's Complete Response with reference to BPM has satisfied the Division's concerns regarding BPM. The information provided supports the conclusion that BPM does not reflect significant underlying pathology.

The incidence of pooled BPM events ranges from 8.1% in placebo-controlled trials to 17.5% in the clinical pharmacology studies, with the majority being of mild or moderate severity, usually reported within 12-48 hours after dosing and spontaneously resolving, without sequelae, within 24 hours of onset and despite continued dosing. This suggests the absence of serious underlying medical conditions. Although the severity of BPM is reported as severe in 4-5% of subjects it rarely led to discontinuation of drug or required use of narcotic analgesia. The prevalence of BPM tended to decline over time, despite continued exposure. No patient had a serious AE or required hospitalization as a consequence of BPM.

Among patients presenting with BPM (including those with renal disease), physical examinations, imaging, or laboratory testing failed to detect any significant abnormalities or pathology associated with these events.

Recommendations Concerning Dose

It is recommended that the sponsor propose lower than standard doses for patients with moderate renal impairment.

Recommendations on Labeling

It is recommended that the labeling indicate that BPM may be severe in <5% of patients, and may require the use of narcotic analgesia

Overall assessment of the response:

The sponsor has adequately explored the effects of tadalafil on back pain and myalgia. Although the etio- pathogenesis of this adverse event remains unknown, it is unlikely to be associated with serious underlying pathology. The label should include the following:

1. Based upon pharmacokinetic and clinical safety information, the dose of tadalafil should be limited to 5 mg not more than once daily in patients with moderate and

severe renal insufficiency or end-stage renal disease. The maximum dose recommended for patients with moderate or severe renal insufficiency should be 10 mg; and at that dose in this population, CIALIS should be taken not more than once in every 48 hours.

2. Back pain or myalgia generally occurred 12 to 24 hours after dosing and it generally resolved within 48 hours of onset. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbancy. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported infrequently (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective. Mild narcotics (e.g. codeine) were given in approximately 5-10% of cases where medical treatment was required. Overall, approximately 0.5% of all tadalafil-treated subjects discontinued treatment as a consequence of back pain. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology.

3.5. Assessment of Cardiovascular Events

Clinical Deficiency #1 under other "Additional Recommendations" stated:

"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[actually Subject 003-4065], 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.”

Regulatory History

In 03 June 2002, in the Brief Document for the post-approvable action meeting, Lilly ICOS made a proposal to provide an analysis of the medically significant cardiovascular adverse events, to make further attempts to obtain the subject specific serious adverse event (SAE) data, and to submit Studies LVBZ and LVCP within 3 months of the meeting. DRUDP minutes from the 03 June 2002 post-approvable action meeting stated, “the proposal is acceptable.”

In 28 June 2002, the final study report LVCP (Exercise Tolerance) was submitted. In 06 August 2002, the final study report LVBZ (Coronary Blood Flow) was submitted. In 04 March 2003, a Pre-Complete Response Guidance meeting was held. The FDA minutes stated that the DRUDP clinical review team requests an analysis, based on frequency of reported events, of all cardiovascular events for the placebo-controlled studies.

Sponsor’s Response

The sponsor provided a retrospective analysis of potentially clinically significant cardiovascular adverse events and updated subject narratives. The sponsor also submitted a summary of the results of Studies LVCP and LVBZ. The primary reviewer for this response was Dr Harry Handelsman.

3.5.1. Executive Summary for the Cardiovascular Issues:

Summary of Clinical Findings

1. Cialis is well tolerated and is not associated with an increased incidence of potentially clinically significant cardiovascular AE’s.
2. A review of the comprehensive case summaries and supplementary material failed to reveal new clinically significant findings.

3. A review of Studies LVBZ and LVCP supported the conclusions that in subjects with CAD, Cialis had no adverse effect on myocardial blood flow either at rest or during pharmacologic stress with dobutamine, and does not reduce time to myocardial ischemia during exercise stress testing.

3.5.2. Clinical Review of the Cardiovascular Issues

The following materials were reviewed:

1. Review of Cardiovascular Events--Complete Response, May 27, 2003.
2. Clinical Study LVBZ. (Effects of Cialis on Myocardial Perfusion Using PET)
3. Clinical Study LVCP. (Effects of Cialis on Exercise Stress Tests in Men with CAD)
4. Tadalafil Periodic Safety Update Report, June 2, 2003.
5. Minutes of the June 3, 2002 Guidance Meeting.
6. Sponsor's Information Amendment, August 19, 2003.

Clinical Review Methods:

The clinical trials LVBZ and LVCP were reviewed in detail. Other material noted above, including comprehensive case summaries of subjects with serious AE's or potentially significant cardiovascular AE's noted in the Complete Response were also reviewed in detail. Cardiovascular events included the following 11 categories;

1. Cardiac Arrest
2. Myocardial Infarction/Ischemia/Possible Ischemia
3. Congestive Heart Failure
4. Ventricular Arrhythmias
5. Syncope/Hypotension/Possible Hypotension
6. Other Cardiovascular Events Including Pulmonary Embolism and Pulmonary Hypertension
7. Supraventricular Arrhythmias
8. Other Arrhythmias
9. Conduction Defects
10. Subjective Rhythm/Heart Rate

11. Cerebrovascular Events

3.5.3. Clinical Results:

In 50 clinical pharmacology studies (N=1582) using doses ranging from 2.5-100mg of Cialis, and 26 double-blind clinical studies (N=3666), excluding 3 long-term open-label studies without placebo, the incidence of cardiovascular events was 1.58% and 1.64% respectively, versus placebo (N=476) 3.2% and (N=1437) 1.81% respectively. Results from the clin-pharm studies are summarized in Table 10.

Table 10: Incidence of Cardiovascular Events, Clinical Pharmacology Studies

Treatment Group	N	Incidence	
		N	%
Placebo	476	15	3.2
Tadalafil 2.5mg	16	0	0
Tadalafil 5.0 mg	195	1	0.5
Tadalafil 10 mg	930	15	1.6
Tadalafil 20 mg	364	8	2.2
Tadalafil 40 mg	45	0	0
Tadalafil 50 mg	14	1	7.1
Tadalafil 100 mg	18	0	0

The 3 long-term open-label studies (LVBD, LVBL, LVDR) recorded 87 cardiovascular events among 1707 subjects (4.7%).

In placebo-controlled trials, the majority of AE's in both the placebo- and Cialis-treated groups occurred within 48 hours of last dose, and most subjects were within 3 days of the most recent dose. The distribution of AE's was similar between drug and placebo.

Table 11: Cardiovascular AE's in 29 Clinical Studies

	Cialis (N=4400)		Placebo (N=1437)	
	N	%	N	%
Cardiac arrest	4	0.1	0	0
MI/ Ischemia	62	1.4	15	1.1
CHF	2	0.05	1	0.07
Ventricular Arrythmia	2	0.05	1	0.07
Syncope or Hypotension	12	0.27	6	0.42
SupraVentricular Arrythmia's	6	0.15	1	0.07
Other Arrythmia's	6	0.15	0	0
Other CVE's	2	0.05	0	0
Conduction defects	6	0.15	1	0.07
Cerebrovascular Events	11	0.25	0	0
Subjective /Rhythm	45	0.99	6	0.42

3.5.3.1. Deaths

The sponsor has provided patient narratives and summaries for the 11 deaths, of any cause, in subjects who participated in any of the clinical studies; with the exception of 1 subject, in an ongoing study (LVCI) who died a few months after discontinuation from that study, and whose patient narrative is presently unavailable. (There were no deaths in the clin-pharm studies). The investigators concluded that in 9 of the cases the cause of death was unrelated to study drug or protocol procedures, and that 1 cardiac arrest and death was “possibly” related.

Reviewer’s Comments: This reviewer disagrees with investigator’s conclusion in 6 of the 10 cases of death, as follows:

1. Patient 007-3072 was found dead in his sleep. The investigator reported the death as “cardiac arrest unrelated to study drug.” An autopsy was performed and the results are pending. In the absence of further evidence exonerating Cialis, I believe the cause of death should be stated as “possibly related” to study drug.
2. Patient 003-4065 collapsed shortly after playing golf. The subject had a prior history of a MI, and the investigator reported the death as “cardiac arrest unrelated to study drug.” Additional information regarding details surrounding the event,

including drug reconciliation and autopsy report are pending, and I believe the cause of death should be stated as “possibly related” to study drug.

3. Patient 105-2107 was described as having a cardiac arrest 2 weeks following hospitalization after a MI requiring resuscitation. The investigator’s assessment was that the event was unrelated to study drug because there were cardiovascular risk factors present. The presence of risk factors can indeed be regarded as factor in proposing a causal pathway for AE’s, but cannot rule out the possibility that the study drug also played a role in this pathway.
4. Patient 100-1016 was found dead at home 4 days after hospital discharge following a right radical nephrectomy. The investigator was unsuccessful in attempts to obtain study diaries and resolve study drug reconciliation, and did not consider the death related to Cialis. This reviewer concludes that the death is possibly related to study drug.
5. Patient 602-6077 suffered a fatal cardiac arrest which occurred during exercise in a gym approximately 45 minutes after his last dose of Cialis 20 mg. An autopsy confirmed that the death resulted from preexisting coronary atherosclerosis, and the investigator reported the death as unrelated to study drug or protocol. I believe it reasonable to conclude that the event was possibly related to study drug.
6. Patient 010-1453 suffered an acute MI followed by cardiogenic shock, multiple arrhythmias, and a fatal cardiac arrest. The subject’s study drug diary was unobtainable, however the study drug package indicated that a dose of drug was taken sometime during the 9 days prior to death. Contrary to protocol instructions, the subject took a dose of comparator ED drug 1 hour prior to the onset of symptoms. Given that the time of last dose of study drug could not be determined, this reviewer cannot agree with the investigator’s assessment that the event is unrelated to study drug.

3.5.3.2. Serious Adverse Events: Notable Case Studies from Clinical Trials:

1. Patient 102-2036, 69 years old, had a diagnosis of MI 14 days following his last dose of Cialis 20 mg. He subsequently had successful angioplasty and was discontinued from study due to this AE.