

Action Items:

- Meeting minutes to be conveyed within 30 days

Meeting Chair
Mark Hirsch, M.D.
Medical Team Leader

Meeting Recorder
Dornette Spell-LeSane, NP-C
Regulatory Project Manager

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/s/

Mark S. Hirsch
4/15/02 02:41:08 PM
I concur

Memo

To: Daniel Shames, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Nora Roselle, Pharm.D.
Safety Evaluator, Office of Drug Safety
HFD-400

Through: Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: Dornette Spell-LeSane
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

Date: February 19, 2002

Re: ODS Consult 00-0120-1; Cialis (tadalafil), 20 mg tablet; NDA 21-368

This memorandum is in response to a January 29, 2002, request from your Division for a second re-review of the proprietary name, Cialis. The proposed proprietary name, Cialis, was found unacceptable by ODS in the initial name review on October 5, 2000 (Consult 00-0120). The drug was still in the IND stage when the initial tradename was reviewed by ODS. The tradename "Cialis" was found acceptable in the re-review on January 10, 2002 (Consult 00-0120) as the drug became an NDA and the sponsor submitted new information on the drug product to the Agency. The action date for this application is April 28, 2002.

ODS has not identified any additional proprietary or established names that have the potential for confusion with Cialis since we conducted our initial re-review on January 10, 2002 (Consult 00-0120), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

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/s/

Nora L. Roselle
2/22/02 09:30:43 AM
CSO

Jerry Phillips
2/22/02 09:35:03 AM
DIRECTOR



NDA 21-368

INFORMATION REQUEST LETTER

Lilly Research Laboratories
Attention: Gregory Brophy, PhD
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

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

We are reviewing the Clinical Pharmacology and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical Pharmacology:

1. Please indicate which isozymes of UDP-glucuronosyltransferase are involved in the glucuronidation of catechol and methylcatechol metabolites of tadalafil. If this glucuronidation reaction is blocked, how will it affect the exposure of the active moieties and subsequently the safety and efficacy of tadalafil?"

Drug substance:

1. Per ICH-Q6A, the acceptance criteria for "Total related substances" should be tightened to NMT 0.1%, unless justified.
2. Please submit justification for not providing microbial limit specification.
3. Provide the summary of manufacturing, characterization, testing, COA, and storage information for IC351 Corporate Reference Standard and LY 450190 reference standard. Please clarify if these standards were calibrated against the Lot 131UM8.
4. For the "_____ HPLC method in drug substance", a system suitability parameter (_____) should be determined.
5. Provide the results of USP testing (_____) used to store the drug substance.
6. The proposed 24-month of re-test period is not acceptable. _____ month of re-test period is granted.
7. Provide the following information on the drug substance labels:
 - a. Name of the drug substance
 - b. Lot number, weight, manufacturing date and date of release.
 - c. Caution statement per 21 CFR 201.120.

Drug product:

1. Per ICH-Q6A, the acceptance criteria for "Total related substances" and "Largest individual related substances" should be tightened to NMT 0.1%, and NMT 0.1%, respectively, unless justified.
2. The proposed expiry date of 24 months is not acceptable. Based on available data, _____ month of expiry date is granted for the product packaged in bottles and blisters packaging configurations.
3. The stability data indicate that dissolution rate failed the acceptance criteria at _____ Clarify if _____ testing were performed and passed.
4. Submit justification for not providing microbial limit specification.
5. In accordance with 21 CFR 314.50(e)(2)(i), provide three copies of the method validation package.
6. Provide the following information on storing the bulk tablets in the _____:
 - a. Storage temperature
 - b. Time period for which the tablets were stored before the packaging.
7. Post approval stability commitment is not satisfactory and must include the following statements:
 - a. The first three production lots in each packaging configuration will be placed on stability at 25°C/60%RH and tested at 0, 3, 6, 9, 12, 18, and 24, and annually thereafter. The same batches will be tested at _____
 - b. A minimum of one lot per year (commercial strength) in each packaging configuration will be placed on stability at 25°C/60%RH and tested annually and stability results will be submitted in annual reports.
 - c. Withdraw from the market any batches found to fall outside the approved acceptance criteria for the drug product and report the change or deterioration to the FDA under 21CFR314.51(b)(1)(ii).
 - d. Extension of expiry date will be based on real time data of commercial production batches in each container/closure system.
8. Provide the following information:
 - a. Labels for bottles and cartons _____
 - b. Labels for blisters and cartons _____
9. Clarify the inclusion of " _____ " entries on the label.

NDA 21-368
Information Request
Page 3

If you have any questions, call Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jeanine Best
2/11/02 11:22:58 AM
Signing for Terri Rumble

MEMORANDUM OF TELECON

DATE: February 7, 2002

Time: 5:06 p.m.

APPLICATION NUMBER: NDA 21-368, Cialis (tadalafil) tablet

BETWEEN:

Name: Cathi Melfi, US Regulatory Affairs

Phone: 317-433-5287

Representing: Lilly ICOS LLC

AND

Name: Dornette Spell-LeSane, NP-C, MHA,
Regulatory Project Manager
Rajiv Agarwal, Ph.D., Chemistry Reviewer
Division of Reproductive and Urologic Drug Products
HFD-580

SUBJECT: Chemistry request for information

Background:

Cialis (tadalafil) is a PDE5 inhibitor currently under review in the Division for the indication of erectile dysfunction. The PDUFA goal date is April 29, 2002. The Chemistry Reviewer requested a teleconference with the sponsor to request additional information to assist in the evaluation of this drug product.

Discussion:

- sponsor should provide raw dissolution data for the individual tablets

Decisions reached:

- the sponsor agrees to discuss this request with their chemistry team and provide the requested information to the Division for review

Action Items:

- Meeting minutes to be conveyed within 30 days

Meeting Chair
Rajiv Agarwal, Ph.D.
Chemistry Reviewer

Meeting Recorder
Dornette Spell-LeSane
Regulatory Project manager

SEE ADDENDUM:

Addendum to the Meeting Minutes

Date: February 11, 2002

FDA Representatives:

Rajiv Agarwal, Ph.D., Chemistry Reviewer
Dornette Spell-LeSane, Regulatory Project Manager

Lilly ICOS Representatives:

Catherine Melfi, Ph.D., Regulatory Affairs
Bill Kluttz, Chemistry

Purpose: To provide clarification of the February 7, 2002, chemistry request for information.

Background:

The sponsor requested this teleconference to obtain clarification of the chemistry request regarding the dissolution data.

Discussion:

- DRUDP clarified the request for information regarding the dissolution data
- the sponsor should provide:
 - batch numbers used to determine dissolution specifications
 - raw data of dissolution for _____
 - rationale to support variability in release rates at _____

Decisions reached:

- the sponsor understands the request and will provide information in an Excel spreadsheet format

Meeting Chair
Rajiv Agarwal, Ph.D.
Chemistry Reviewer

Meeting Recorder
Dornette Spell-LeSane
Regulatory Project manager

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/s/

Dornette Spell-LeSane
3/5/02 03:15:23 PM
CSO

Rajiv Agarwal
3/5/02 03:18:29 PM
CHEMIST

Internal Meeting Minutes

Date: February 7, 2002 **Time:** 1:00 pm-2: 00 p.m. **Location:** Parklawn; 17B-43

Drug: Cialis (tadalafil) 20 mg

Sponsor: Lilly ICOS

Indication: erectile dysfunction

Type of Meeting: 8-month status meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

Mark Hirsch M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

George Benson, M.D., Medical Officer, DRUDP (HFD-580)

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Venkateswar R. Jarugula, Ph.D., Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Sandip Roy, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Rajiv Agarwal, Ph.D., Chemistry Reviewer, (DNDC II) @ DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the reviews for this application

Background:

Cialis (tadalafil), is a potent, selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). Cialis is an oral treatment indicated for erectile dysfunction. The sponsor is requesting approval for a 20 mg dose tablet. This drug was developed under IND 54,553 initially submitted on November 6, 1997. This application, dated June 28, 2001, was received June 29, 2001. This application was filed on August 28, 2001. The 10-month user fee goal date is April 29, 2002, and the 12-month user fee goal date is June 29, 2002. This is the third status meeting.

Discussion:

Goal Dates:

March 25, 2002	reviews are due to the Team Leader
April 8, 2002	reviews are due to the Acting Division Director
April 15, 2002	reviews are due to the Office Director
April 29, 2002	10-month goal date

Outstanding Issues:

- Sperm data is being reviewed by the Medical Officer
- 4-month safety update is being reviewed by the Medical Officer
- additional information has been requested to evaluate QT data; a consult will be forwarded to the Cardio-Renal Division
- Chemistry and Clinical Pharmacology information request letter is circulating for sign off
- Consults pending: Ophthalmology, DDMAC, and OPDRA's 90-day final tradename review

Clinical

- Dr. Batra reports that his review is ongoing
- in reviewing the data to determine the lowest effective dose, the 10 mg efficacy is very similar to the 20 mg; considerations for 10 mg should be examined
- Dr. Benson provided a brief description of results from trials LVCF, LVCO and LVBK
- the safety review is ongoing, Dr. Benson described a few cases of increased serum LFT's;
- the 20 mg dose was described as appearing "safe"
- preliminary results for the sperm study are "negative"
- preliminary results for the QT interval study are "negative"
- preliminary results for the ophthalmology concerns are negative
- other adverse events include back pain, headache and dyspepsia

Chemistry:

- draft review is completed; deficiency letter is circulating
- EES have been assigned
- DMF reviews are ongoing, (12 completed, one remaining)
- stability data for the 10 mg dose has not been reviewed; chemistry will need to be notified by the Medical Officer if the 10 mg dose will be considered for approval
- dissolution specifications are still being negotiated (tightened)

Clinical Pharmacology and Biopharmaceutics:

- review is ongoing
- on initial inspection it appears that there may be an additive effect on lowering blood pressure with alcohol at 10 mg; no alcohol studies were conducted with the 20 mg dose
- no interaction was noted with antihypertensive amlodipine, metoprolol and tamsulosin, these studies were done using the 10 mg doses
- pharmacodynamic interaction studies conducted at 10 mg cannot be extrapolated to the 20 mg dose
- there is evidence of a benefit, particularly for sub-populations, for the 10 mg dose
- creatinine clearance is an important co-variant for pharmacokinetics, there is a two-fold increase in exposure in those with mild to moderate renal impairment, back pain may be associated with renal impairment
- there is no study in severe renal impairment
- ketoconazol and rifampin interaction studies under review

Statistics: (not present)

- final draft with Team Leader

Pharm-Tox:

- draft review is with Team Leader
- a Pharm-Tox teleconference was held February 6, 2002; DRUDP reported that the Executive CAC approved the dose levels in the ongoing 2-year carcinogenicity studies in mice and rats based on the AUC ratios between rodents and humans at the 10 mg dose; when the dose under investigation was increased to 20 mg the AUC ratio decreased 4-fold; therefore, the doses for both sexes of mice and male rats are not valid based on exposure ratios
- the sponsor was requested to conduct a study using radioactive drug to demonstrate saturation of absorption; alternatively, the sponsor could measure metabolites in plasma with increasing doses; the sponsor was requested to submit this data for review as soon as available before the goal date
- the reviewer reported that depending on the results of the mentioned study, an alternate mouse study may be recommended as a Phase 4 commitment

DSI

- Inspections of two sites are pending

OPDRA Trademark Review

- January 29, 2002, 90-day final tradename review is pending; OPDRA's preliminary review was completed on January 10, 2002, found the tradename acceptable

Labeling:

- DDMAC review is pending
- a separate labeling meeting will be scheduled
the team will be notified

**labeling meeting scheduled for March 21, 2002
at 2:30 p.m.**

Action Items:

None

Next Meeting scheduled for March 7, 2002, 10:00 a.m.

Minutes Preparer:

Meeting Chair

cc:
Original
HFD-580/Div. Files
HFD-580/

Drafted by: Spell-LeSane, 2.28.02
Concurrence: /Parekh, Ashok, Agarwal, 3.5.02/Hirsch, 4.10.02
final: Spell-LeSane, 4.16.02

8-month Status Meeting Minutes
Cialis
February 7, 2002
Page 4

MEETING MINUTES

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/s/

Mark S. Hirsch
4/17/02 02:28:28 PM

MEMORANDUM OF TELECON

DATE: February 6, 2002

Time: 12:30 p.m.

APPLICATION NUMBER: NDA 21-368, Cialis (tadalafil) tablet

BETWEEN:

Name: Cathi Melfi, US Regulatory Affairs
Pete Sausen, Toxicology
Diane Phillips, ADME
Greg Brophy, Director, US Regulatory Affairs
Susan Sullivan, Regulatory Affairs

Phone: 317-433-5287
Representing: Lilly ICOS LLC

AND

Name: Dornette Spell-LeSane, Regulatory Project Manager
Alex Jordan, Ph.D., Pharmacology Team Leader
Yangmee Shin, Ph.D., Pharmacology reviewer
Division of Reproductive and Urologic Drug Products,
HFD-580

SUBJECT: To discuss issues related to the Pharmacology-Toxicology review of the carcinogenicity studies

Background:

Cialis (tadalafil) is a PDE5 inhibitor currently under review in the Division for the indication of erectile dysfunction. The PDUFA goal date is April 29, 2002. The Pharmacology Team Leader requested a teleconference with the sponsor to discuss the carcinogenicity data for this drug.

Discussion:

- DRUDP reported that the Executive CAC approved the dose levels in the ongoing 2-year carcinogenicity studies in mice and rats based on the AUC ratios between rodents and humans at the 10 mg dose; when the dose under investigation was increased to 20 mg the AUC ratio decreased 4-fold; therefore, the doses for both sexes of mice and male rats are not valid based on exposure ratios
- the Saturation of absorption was demonstrated for the parent compound; the Division would like to know what information is available that demonstrates that saturation of absorption was achieved for the metabolites as well
- the sponsor stated that they examined the ratios of parent to metabolites in metabolism studies, but did not have direct metabolite data demonstrating saturation of exposure

- DRUDP strongly recommends that Lilly conduct a study using radioactive drug to demonstrate saturation of absorption; alternatively, the sponsor could measure metabolites in plasma with increasing doses
- DRUDP requested that these studies be conducted and submitted to the Agency prior to the goal date; this submission will not be regarded as a major amendment
- If saturation absorption is not achieved, an alternative model carcinogenicity study, for example, — would be required as a Phase 4 commitment

Decisions reached:

- the sponsor agrees to conduct and submit the results of the total radioactivity study prior to the goal date
- the sponsor may submit the proposal for conducting these studies for review and comment prior to study initiation

Action Items:

- sponsor to submit proposal for total radioactivity studies within the next 2-weeks
- Meeting minutes to be conveyed within 30 days

Alex Jordan, Ph.D.
Pharmacology Team Leader

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/s/

Dornette Spell-LeSane
2/28/02 09:22:25 AM
CSO

Alexander W. Jordan
2/28/02 10:18:45 AM
PHARMACOLOGIST

Internal Meeting Minutes

Date: January 14, 2002 **Time:** 1:00 pm-2: 00 p.m. **Location:** Parklawn; 17B-43

Drug: Cialis (tadalafil) 20 mg tablet

Sponsor: Lilly ICOS

Indication: erectile dysfunction

Type of Meeting: 7-month status meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

Mark Hirsch M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

George Benson, M.D., Medical Officer, DRUDP (HFD-580)

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

David Hoberman, Ph.D., Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Sandip Roy, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580),

Rajiv Agarwal, Ph.D., Chemistry Reviewer, (DNDC II) @ DRUDP (HFD-580)

Diane Moore, BS, Acting Chief, Project Management Staff, DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the reviews for this application

Background:

Cialis (tadalafil), is a potent, selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). Cialis is an oral treatment indicated for erectile dysfunction. The sponsor is requesting approval for a 20 mg dose tablet. This drug was developed under IND 54,553 initially submitted on November 6, 1997. This application, dated June 28, 2001, was received June 29, 2001. This application was filed on August 28, 2001. The 10-month user fee goal date is April 29, 2002, and the 12-month user fee goal date is June 29, 2002. This is the second status meeting.

Discussion:

Clinical

- Dr. Batra reports that his review is ongoing
- 4-month safety data has been received, contents have not yet been inspected
- request for additional safety data related to QT interval is pending and expected to arrive this week
- ophthalmology consult was sent on October 29, 2002, and is pending

Labeling:

- no Patient package insert was submitted with the NDA
- sponsor states that they do not plan to submit a patient package insert for this application
- PM request DDMAC investigate if PPI is necessary

Action Items:

Project Manager to prepare Chemistry and Clinical
Pharmacology information request letter by January 31, 2002

Date Completed

Final sign off February 11, 2002

Next Meeting February 7, 2002

Minutes Preparer:

Meeting Chair

cc:

Original
HFD-580/Div. Files
HFD-580/

Drafted by: Spell-LeSane, 2.18.02
Concurrence: Batra, Parekh, 3.5.02/Moore, 3.7.02/Hirsch, 4.10.02
final: Spell-LeSane, April 16, 2002

MEETING MINUTES

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/s/

Mark S. Hirsch
4/17/02 02:21:06 PM

**Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 31, 2001
NDA NUMBER: 21-368 (IND 54-553)
NAME OF DRUG: Cialis (tadalafil tablets), 20 mg
NDA HOLDER: Lilly ICOS LLC

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for a re-assessment of the tradename "Cialis", regarding potential name confusion with other proprietary/established drug names. The tradename "Cialis" was found unacceptable in a prior review on October 5, 2000 (OPDRA Consult 00-0120). This drug was still in the IND stage when the tradename "Cialis" was reviewed. "Cialis" is now an NDA and the sponsor has submitted to the Agency new information on this drug product.

PRODUCT INFORMATION

"Cialis" is the proprietary drug name for tadalafil tablets and is indicated for the treatment of erectile dysfunction. When sexual stimulation causes the local release of nitric oxide, tadalafil inhibits PDE5, which causes levels of cGMP to increase in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation. "Cialis" will be available as a 20 mg tablet, which is different than what was stated in the IND application (10 mg tablet). The recommended dose of "Cialis" is 20 mg prior to sexual activity. It has been proven to be effective up to 36 hours after dosing and, in some patients, as early as 16 minutes after dosing. The maximum dose is 20 mg per day. "Cialis" is contraindicated for patients who are using any form of organic nitrates.

II. RISK ASSESSMENT:

The proprietary name review (OPDRA Consult 00-0120), dated October 5, 2000, found the proposed proprietary name "Cialis" unacceptable based on the similarities between *Claritin* 10 mg and "Cialis" 10 mg. The sponsor recently submitted new information where "Cialis" will now be available as a 20-mg tablet instead of a 10-mg tablet. Since there is no longer an existence of an overlapping strength, the potential risk of a medication error occurring between these two drug products is decreased. If *Claritin* 10 mg was dispensed mistakenly instead of "Cialis" 20 mg and the directions were adjusted to fit a 20 mg dose (take 2 tablets once a day), the pharmacist would realize that a mistake had occurred since the recommended dose of *Claritin* is 10 mg once a day. However, if a *Claritin* or a "Cialis" prescription was not written with a strength, the directions of use would still distinguish these two drug products. The directions on a "Cialis" prescription would generally state "Take 1 tablet before sexual activity. Maximum 1 tablet a day." The directions on a *Claritin* prescription would just state "Take 1 tablet

daily." If a *Claritin* prescription was mistaken for "Cialis", it would seem odd to a pharmacist for a patient to take an erectile dysfunction medication every day. If a "Cialis" prescription was mistaken for *Claritin*, it would seem more odd to a pharmacist that a patient needs to take an antihistamine medication before sexual activity. The differences in these dosing directions would decrease the potential risk of a medication error occurring.

Aralen was also mentioned in the prior consult where it found that the potential risk of a medication occurring between *Aralen* and "Cialis" is low. The new information supplied by the sponsor for "Cialis" does not change the level of potential risk for a medication error occurring between these two drug products.

From the new information given by the sponsor, ODS does not have any objections to the use of the proprietary name "Cialis".

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER LABEL (20 mg; 30 tablets)

1. The dosage form "tablets" should appear after the established name.
2. The statement "See accompanying literature for dosage" should be revised to state "Usual dosage: Take 1 tablet daily. See package insert."
3. We find the NDC number difficult to read. We suggest that it be increased in prominence.
4. " —————" is not necessary and could be deleted.

IV. RECOMMENDATIONS:

- #### A. DMETS has reconsidered its previous recommendations and has no objections to the use of the proprietary name "Cialis".

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's/ANDA's from this date forward.

- #### B. DMETS recommends the above labeling revisions to encourage the safest possible use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Jennifer Fan
1/8/02 09:52:32 AM
PHARMACIST

Carol Holquist
1/10/02 10:47:16 AM
PHARMACIST

Jerry Phillips
1/10/02 11:07:36 AM
DIRECTOR

Internal Meeting Minutes

Date: December 12, 2001 **Time:** 3:00 pm-4: 00 p.m. **Location:** Parklawn; 17B-43

Drug: Cialis (tadalafil) 20 mg tablet

Sponsor: Lilly ICOS

Indication: erectile dysfunction

Type of Meeting: 6-month status meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

Mark Hirsch M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

George Benson, M.D., Medical Officer, DRUDP (HFD-580)

David Hoberman, Ph.D., Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Yangmee Shin, Ph.D., Pharmacology Reviewer, DRUDP (HFD-580)

Venkat Jarugula, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

Sandip Roy, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Rajiv Agarwal, Ph.D., Chemistry reviewer, (DNDC II), @ DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)

Meeting Objectives: To discuss the review status of this NDA application for Cialis

Background:

Cialis (tadalafil), is a potent, selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). Cialis is an oral treatment indicated for erectile dysfunction. The sponsor is requesting approval for a 20 mg dose tablet. This drug was developed under IND 54,553 initially submitted on November 6, 1997. This application, dated June 28, 2001, was received June 29, 2001. This application was filed on August 28, 2001. The 10-month user fee goal date is April 29, 2002, and the 12-month user fee goal date is June 29, 2002. This is the first status meeting.

Discussion:

Clinical

- the Medical Team Leader reported for Dr Batra (not present) that the medical officer's review is ongoing
- the ophthalmology consult was sent October 29, 2001
- the 4-month safety update has been submitted; it is expected that the 20 mg sperm study (LVCD) is in the safety update
- discussion regarding the contents of the final safety update is ongoing

OPDRA Trademark Review

- review is pending

Labeling:

- labeling not discussed

Action Items:

- Project Manager to request the sponsor identify where in the NDA submission relevant data for QT studies can be found, sponsor to provide pages and volume numbers

Next Meeting January 14, 2002

Date Completed

December 14, 2001 request made via teleconference with sponsor

Minutes Preparer:

Meeting Chair

cc:
Original
HFD-580/Div. Files
HFD-580/

Drafted by: Spell-LeSane, 2.18.02
Concurrence: Agarwal, Jarugula, Shin, 3.5.02/Hirsch, 4.10.02
final: Spell-LeSane, 4.16.02

MEETING MINUTES

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/s/

Mark S. Hirsch
4/17/02 02:17:11 PM

Spell Lesane, Dornette D

From: Lewin, Constance
Sent: Friday, October 05, 2001 9:27 AM
To: Spell Lesane, Dornette D; Batra, Ashok
Subject: Cialis clinical inspections

Hi, Dornette & Ashok

Dornette mentioned that there are four foreign sites for inspection. Please note that, in general, DSI only conducts two foreign inspections per application. If there are extraordinary circumstances warranting inspection of an additional two sites, let's talk about it.

Thanks,

Connie

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

Date: October 4, 2001

To: Constance Lewin, M.D., Medical Officer
Good Clinical Practice 1, HFD-46
Division of Scientific Investigations

Through: John Martin M.D., Branch Chief
Good Clinical Practice 1, HFD-46

From: Dornette Spell-LeSane, NP-C, M.H.A., Project Manager,
Division of Reproductive and Urologic Drug Products (HFD-580)

Through: Daniel Shames, M.D., Acting, Division Director
DRUDP; (HFD-580)

Subject: Request for Clinical Inspections for NDA 21-368

As discussed, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority. This NDA Cialis (IC351, tadalafil) is a PDE5 inhibitor, indicated for the treatment of erectile dysfunction. This product is classified as a new molecular entity. The contact person for Lilly-ICOS is Cathi Melfi, (317) 277-2905.

Indication	Pivotal Protocol #	Investigator's Name/Address
<u>Erectile Dysfunction</u>	<u>H6D-MC-LVDJ</u>	 <hr/> <hr/>

The address and phone numbers of the above investigators have been requested.

We have requested the international inspection because (please check appropriate statements):

- There are insufficient domestic data; or
- Only foreign data are submitted to support an application; or

NDA 21-368
DSI request
Page 2

- ___ Domestic and foreign data show conflicting results pertinent to decision-making; or
- ___ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

We request that the inspections be performed and the Inspection Summary Results be provided on or before February 1, 2002. We intend to make a regulatory decision on this application by March 11, 2002. The 10-month user fee goal date is April 29, 2002.

Should you require any additional information please contact Dornette Spell-LeSane, NP-C, M.H.A. at 301-827-7514.

Concurrence: Rumble, Shames, 10.4.01

Distribution:
NDA 20-582
HFD-580/Division File
HFD-580/Spell-LeSane, Hirsch, Batra, Shames, Rumble, Olmstead
HFD-344/Lewin

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/s/

Daniel A. Shames
11/19/01 01:59:45 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: August 28, 2001

TO: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly ICOS

FROM: Dornette Spell-LeSane, NP-C, M.H.A.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, (HFD-580)

SUBJECT: **4-month Safety Update**
NDA 21-368, Cialis (tadalafil) 20 mg

Please refer to your amendment dated August 14, 2001, containing a Format and Content proposal for the NDA 4-Month Safety Update. We have reviewed the proposal and have the following comments:

1. The proposal to not integrate new safety data (which represents less than a 25% increase in subjects exposed) with the original NDA data analysis is acceptable.
2. The proposal to include (1) overview of safety update, (2) table of new ongoing studies and (3) a summary of additional subjects exposed to IC351, since preparation of the original NDA, is acceptable.
3. The proposal to provide listings of deaths, serious adverse events, and discontinuations due to adverse events that have occurred, since the time of preparation of the original NDA, is acceptable. In addition, please add a listing of the overall adverse events for the 235 new patients and "re-calculate" the overall adverse events in those ongoing patients who have had four months more drug exposure since the time of the original NDA.

If you have any questions please call me at 301-827-7514.

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/s/

Dornette Spell-LeSane
8/29/01 04:09:30 PM
CSO

Daniel A. Shames
8/29/01 04:42:05 PM
MEDICAL OFFICER

Filing Meeting Minutes

Date: August 20, 2001 **Time:** 2:00 pm-3: 00 p.m. **Location:** Parklawn; 17B-43

Drug: Cialis (tadalafil) 20 mg

Sponsor: Lilly ICOS

Indication: erectile dysfunction

Type of Meeting: Filing Meeting

Meeting Chair: Daniel Shames, M.D.

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

Daniel Shames, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Mark Hirsch M.D., Medical Team Leader, DRUDP (HFD-580)

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

Brenda Gierhart, M.D. Medical Officer, DRUDP (HFD-580)

David Hoberman, Ph.D., Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Jeanine Best, RN, MSN, Sr. Regulatory Associate, DRUDP, (HFD-580)

Yangmee Shin, Ph.D., Pharmacology Reviewer, DRUDP (HFD-580)

Constance Lewin, M.D., Division of Scientific Investigations

Venkat Jarugula, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Eric Duffy Ph.D., Deputy Director, Office of New Drug Chemistry (ONDC; HFD-800)

Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)

Meeting Objectives: To discuss the filing status of Cialis

Background:

Cialis (tadalafil), is a potent, selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). Cialis is an oral treatment indicated for erectile dysfunction. The sponsor is requesting approval for a 20 mg dose tablet. This drug was developed under IND 54,553 initially submitted on November 6, 1997. An End-of-Phase 2 meeting was held with the sponsor on August 30, 1999, a CMC Pre-NDA meeting was held November 14, 2000, and a Pre-NDA meeting was held February 21, 2001. This application, dated June 28, 2001, was received June 29, 2001. The filing date for this application is August 28, 2001. The 10-month user fee goal date is April 29, 2002, and the 12-month user fee goal date is June 29, 2002.

Discussion:

Clinical

- Review issues: claims regarding efficacy for diabetic patients, duration of treatment, effect of Cialis on sperm concentration (sperm study to be submitted four months after submission date), effect on vision, effect on special populations such as those with hepatic insufficiency
- NDA is filable

Chemistry:

- This drug is considered a new molecular entity (NME)
- HPLC is used for identification
- additional data may be required for stability; for example, 6 months at room temperature for the 20 mg; adequate stability data is also available for the 10 mg dose
- documentation regarding acceptability of tadalafil by USAN should be provided
- a sample of the drug product should be provided
- NDA is filable

Clinical Pharmacology and Biopharmaceutics:

- the formula used in the clinical trial is identical to the to-be-marketed product
- clinical pharmacology and biopharmaceutics issues will be addressed in the label
- information regarding the metabolite, catechol will be requested
- dosage administration of no more than one/day or two/day should be evaluated, due to the drugs long ½ life
- NDA is filable

Statistics:

- ---
- statistical issues will be addressed in the label
- NDA is filable

PharmTox:

- the sponsor has conducted 1-year dog and 2-year carcinogenicity studies
- a statistical review of carcinogenicity studies will be requested
- toxicity is not apparent
- NDA is filable

Financial disclosure:

- appropriate information was provided to evaluate financial disclosure
- adequate documentation was submitted to comply with 21 CFR 54; the two investigators that reported disclosable information did not enroll a majority of patients at their sites, and therefore, it is unlikely that outcome of the trials was biased
- DSI inspections should be assigned appropriately
- NDA is filable

DSI

- inspection request is pending
- no outstanding issues related to this company or application

OPDRA Trademark Review

- the sponsor submitted request for review under IND ; initially the name was not acceptable and OPDRA agreed to evaluate the sponsor's market research; review is pending

Other:

An advisory committee meeting is not anticipated for this NDA review

Action Items:

- Project Manager to
 1. request the following from the sponsor:
 2. documentation of USAN certification
 3. additional stability data for 20 mg dose
 4. samples of the to-be-marketed product (tablets)
 5. information on the pharmacological activity of the catechol metabolite
 6. request study number of ophthalmology studies
- request ophthalmology consult
- re-submit trademark for OPDRA review
- request statistical consult for review of carci studies
- submit DSI request
- Reviewers should enter filing memo into DFS

Date to be completed

September 14, 2001

October 29, 2001

October 14, 2001

October 5, 2001

October 4, 2001

Minutes Preparer:

Meeting Chair

cc:

Original
HFD-580/Div. Files
HFD-580/

Drafted by: Spell-LeSane, 2.18.02

Concurrence: Best, Batra, 3.7.02

final: Spell-LeSane, 4.13.02

MEETING MINUTES

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/s/

Daniel A. Shames
4/17/02 09:26:58 AM



NDA 21-368

Lilly ICOS
Attention: Gregory Brophy, Ph.D.
Director
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Cialis (IC351, tadalafil) 20 mg tablets
Review Priority Classification:	Standard (S)
Date of Application:	June 28, 2001
Date of Receipt:	June 29, 2001
Our Reference Number:	NDA 21-368

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 28, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 29, 2001 and the secondary user fee goal date will be June 29, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a

"Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Dornette Spell-LeSane, NP-C
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Dornette Spell-LeSane
7/10/01 09:51:36 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>Lilly ICOS LLC 1209 Orange Street Wilmington, DE 13801</p> <p>c/o Gregory T. Brophy, Ph.D. Director U.S. Regulatory Affairs Eli Lilly and Company Lilly Corporate Center, Indianapolis, IN 46285</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>NDA 21-368</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(317) 277-3799</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p> <p>_____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>3. PRODUCT NAME</p> <p>Cialis</p>	<p>6. USER FEE I.D. NUMBER</p> <p>4124</p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/11/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p>Gregory T. Brophy</p>	<p>TITLE</p> <p>Director U.S. Regulatory Affairs</p>	<p>DATE</p> <p>June 28, 2001</p>
--	--	----------------------------------

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 4/20/01

DUE DATE: 1/4/02

ODS CONSULT #: 00-0120

TO:

Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:

Domette Spell-LeSane
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

PRODUCT NAME:

Cialis (tadalafil tablets)
20 mg

NDA SPONSOR: Lilly ICOS LLC

NDA #: 21-368 (IND 54-553)

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) conducted a re-review of the proposed proprietary name "Cialis" to determine the potential for confusion with approved proprietary and established names as well as pending names.

METS RECOMMENDATION:

DMETS has no objection to the use of the proprietary name, "Cialis".

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's/ANDA's from the signature date of this document. A re-review request of the name should be submitted with the NDA number, the proprietary name, and the goal date.

In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Meeting Objectives:

To discuss the proposed NDA submission for Compound IC351 for treatment of erectile dysfunction.

Background:

IC351 (LY450190) is a selective and potent inhibitor of the cGMP-specific phosphodiesterase, PDE5. Lilly ICOS LLC is currently completing Phase 3 trials with IC351 and intends to submit a new drug application (NDA) for IC351 as a treatment for erectile dysfunction (ED) as early as June 2001. The sponsor submitted a meeting package January 23, 2001, (SN101); additional information was submitted February 2, 2001 (SN102). On February 8, 2001, the division requested additional information to assist in the review of the meeting package and to respond to questions. The response to the questions were received February 15, 2001(SN103).

Discussion:

Question #1

Are the proposed formats and plans (proposed table of contents, Phase 3 study reports, representative selection of proposed tables and statistical analysis plan) acceptable for our Phase 3 studies?

Answer:

Yes, the proposed formats and plans are acceptable

Question #2a

Is the proposed plan for the analysis of 3-month data, for the study LVCQ, including the rationale for not incurring an "alpha spend" in the analysis of the 6-month data, acceptable?

Answer:

- Decisions regarding efficacy will depend largely on the 3-month data
- the integrity of the 6-month data is unknown due to the unblinding at 3-months, therefore, the applicability of the 6-month data will be a review issue and may be supportive data only
- the alpha spend will not apply
- integrity of the 6 month data could affect labeling claims
- sustained efficacy claims will be a review issue
- a 3-month study duration is adequate to demonstrate efficacy

Question #2B

A final study report that includes the analysis of the 6-month data will be completed prior to the 4-month safety update to our NDA submission. If we submit this final report with the 6-month results prior to the 4-month safety update, would this constitute a "major amendment" to our NDA, and would it have an impact in terms of extending the standard PDUFA review clock set at the time of filing?

Answer:

- if the final study report is submitted at or before the 4-month safety update, it will not constitute a major amendment
- the 4-month safety update noted applies to a date 4 months after the NDA is submitted for review, not 4 months before the PDUFA goal date

Question #3

Does FDA agree that our proposed ISE statistical analysis plan outlined in Section 4.2 of the meeting package, will support efficacy of the 20 mg IC351 taken as needed up to once daily?

Answer:

- the proposed statistical analysis plan as outlined is acceptable
- regarding dose response analysis, please submit to the NDA conclusions on explored data in the final decision analysis; this includes dose response information, corrected analysis and the recommended dose analysis
- tables should correspond with the appropriate studies
- the proposed tables present LOCF data, the ISE should include the observed values, presented in a parallel analysis in order to evaluate the impact of dropouts on study results
- if the sponsor plans to aggregate centers, please include in the data set, a column that identifies the center

Discussion:

FDA question: sponsor proposes a 20 mg dose as the dose for which approval will be sought, the division would like to know when the complete data from the studies with the 20 mg dose would be available?

Sponsor response: the sponsor stated that results from the LVBK study demonstrated increased efficacy at the 20 mg dose and noted that they will have complete results on this dose in a couple of weeks

Additional FDA comment:

- given the Phase 3 studies are conducted outside of the US, please provide in the ISE comments on interpretation of cross cultural differences, validation of the efficacy measures, and how data may be applied to the US population
- _____ will be a review issue and further discussions of the protocols may be necessary during the review; including a discussion of multiple testing at multiple time points and clinical relevance of the drug

Question #4

Given the information regarding the results of Study LVCD, along with the proposed timing of the 3-month and 6-month results from Study LVCZ, does the submission of the 6-month LVCZ data with the 4-month safety update represent a "major amendment" to our NDA and will it result in an extension of the standard PDUFA review clock set at the time of filing the NDA?

Answer:

- submission of the 6-month results from the LVCZ study will not be considered a major amendment if submitted at or before the 4-month safety update date (i.e., within 4 months of the initial application submission date)
- the sponsor may be taking a risk submitting the 6-month LVCZ data with the safety update if there are significant results

Question #5

Is the methodology of patient identification and determination of duration acceptable to satisfy requirements for long-term safety data? (see slide "ICH Exposure Numbers, NDA Submission and 4-Month Safety Update)

Answer:

- in regard to safety, at 12 months the proposed patient exposure numbers appear to be half that seen at 6 months
- the expected drop out rate may impact on there not being enough patient exposure numbers to demonstrate safety
- if the ICH exposure requirements for the dose proposed for approval are not met at the time of the submission, this could be a filing issue
- regarding the _____ formulation, it is acceptable to use exposure data for the _____ formulation of higher doses in support of meeting ICH exposure requirements for the proposed dose of the to-be-marketed formulation
- the Division is unable to comment on whether or not the six trials are adequate to demonstrate safety until the data is reviewed

Discussion:

Sponsor states that the expected dropout rate at 6 months is 8-10%

Question #6

Does FDA agree that our proposed ISS statistical analysis plan is acceptable?

Answer:

- the proposed ISS statistical analysis plan is acceptable
- the Division requests that a special safety section be provided in the ISS; this section should include specific adverse events; particularly the incidence and severity of back pain, eye disorders, effect on blood pressure, cardiovascular and cerebrovascular adverse events
- duration of adverse events as it relates to duration of exposure should be included in the safety analysis
- it is acceptable to present incidence of back pain in a graph format but sponsor may make the decision on how to present the data
- sponsor should discuss and present benefit/risk ratio in the NDA

Question #7

Does FDA agree that this package is sufficient to support submission of IC351 (LY450190) as a new agent for the treatment of erectile dysfunction?

Answer:

- the information as it is proposed appears acceptable to support filing of the proposed application, with the caveat that the amount of long-term exposure data could impact the fileability of the application

Question #8

Is our proposal to provide this information only in electronic format acceptable? If paper copies of any publications are required, these can be provided upon request.

Answer

- Yes, providing information in electronic format is acceptable

Question #9

Section 7 of this briefing document provides information regarding our plans for electronic submission of this NDA. Are there any formatting or other specifications FDA would like to clarify regarding the information to be submitted electronically?

Answer:

- the plans for the proposed electronic format is acceptable, the guidance document for industry regarding electronic submissions should be followed
- a PROC CONTENTS (SAS application) format for major efficacy files for the studies should be provided

Question #10

The studies that are covered under the financial disclosure rule are LVBN, LVBK, LVDJ, LVCQ, LVCO, LVCE, LVBX, and LVDL (see Section 8). As agreed to on August 30, 1999, no other studies will be covered by the rule since no single investigator from those studies will make a significant contribution to the demonstration of safety. Is this approach acceptable?

Answer:

- the sponsor's approach to financial disclosure reporting information on the proposed studies is acceptable
- please provide: a table for each study listing the investigators (including sub-investigators), status of disclosure (i.e., received, not received), and the number of patients at each site
- please define efforts to obtain this information (i.e., define "due diligence")
- this information is needed in addition to the certification/disclosure forms required under the rule

Question #11

Lilly ICOS LLC intends to request a waiver from the requirement to submit data in the pediatric population under the final rule "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients (15 Aug. 97)." Is the rationale presented above sufficient information on which to base this request?

Answer:

Yes this appears to be acceptable; a final determination of this issue will be made upon receipt of the waiver request

Other Discussions:

- as summarized in Section 8, Lilly ICOS LLC has requested additional information regarding the OPDRA review of our proposed trademark, "Cialis" (December 13, 2000 SN098)

Division response:

- the Division will not make any decisions regarding the tradename until the NDA has been filed
- the tradename, dose, proposed labeling and carton labels will be submitted to OPDRA for a full review at the time of the submission

- In the previously conducted OPDRA review of the tradename, Claritin and Aralen were the approved named products to which Cialis was compared
- the previous OPDRA review noted incorrect interpretation of the proposed tradename in written inpatient and outpatient studies
- the sponsor may submit testing information; for example, the medication error analysis performed by _____ to OPDRA for review; alternatively, the sponsor may submit the information and at the same time submit an alternative name for review
- the Clinical Pharmacology Biopharmaceutics Division request that *in vitro* interaction studies which provide isoenzymes information _____ be included in the submission

Decisions Reached:

- LVCQ study data will be submitted in the NDA as a 3-month report, the 6-month report will be submitted prior to the 4-month safety update (within 4 months of the initial application submission)
- adequacy of long-term exposure data, as defined by ICH, could be a filing issue
- the sponsor is taking a risk submitting 6-month data from LVCZ with the 4-month safety update
- claims for sustained efficacy will be a review issue
- _____ issue; the sponsor may request a teleconference to discuss this issue further
- the Division does not anticipate an Advisory Committee Meeting for this NDA

Action Items:

- Sponsors to discuss comments provided by the Division and consider recommendations prior to NDA submission
- Meeting Minutes to be conveyed to the sponsor within 30 days

Minutes Preparer:

Meeting Chair

cc:

Original IND 54,553

HFD-580/Div. Files

HFD-580/Allen/Shames/Hirsch/Colangelo/Rumble/Parekh/Batra/Hoberman/Jarugula/Benson/Jordan/

Drafted by: Spell-LeSane, 3.14.01

Concurrence: Rumble, 3.15.01, Jordan, Jarugular, Batra, Hirsch 3.19.01, Hoberman, 3.20.01, Colangelo, Shames, Allen, 3.21.01

final: Spell-LeSane, 3.21.01

MEETING MINUTES

/s/

Dornette Spell-LeSane
3/21/01 03:26:14 PM
CSO

Susan Allen
3/21/01 04:36:10 PM
MEDICAL OFFICER

Meeting Minutes

Date: November 14, 2000 **Time:** 10:30-11:30 AM EST **Location:** Parklawn, 17B-45

IND 54,553 **Drug:** IC351 **Indication:** erectile dysfunction

Sponsor: Lilly ICOS LLC **Type of Meeting:** PreNDA - Chemistry

Meeting Chair: Daniel Shames, MD **External Lead:** Susan Sullivan

Meeting Recorder: Kim Colangelo

FDA Attendees:

Daniel Shames, MD – Acting Deputy Director, Division of Reproductive and Urological Drug Products (DRUDP; HFD-580)

Moo-Jhong Rhee, PhD – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

David Lin, PhD – Review Chemist, DNDC II @ DRUDP (HFD-580)

Kim Colangelo, BS – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

~~_____~~
Martha Kral, PhD – Formulation Scientist

Catherine Melfi, PhD - Regulatory

Sharon Snorek – Analytical Chemist

Susan Sullivan – Regulatory

Sandra Zeckel – Development Project Manager

Meeting Objective: To discuss the chemistry section of the NDA submission planned for 2001.

Background: IC351 is a phosphodiesterase Type 5 inhibitor currently in Phase 3 trials for the treatment of male erectile dysfunction. Discussion topics were submitted in a briefing document dated October 13, 2000 (IND 54,553, serial number 090.) The format of this meeting was revised to a teleconference per agreement between Lilly ICOS and DRUDP on November 7, 2000.

Discussion:

Discussion Topic 1: Drug Substance Packaging

- [_____]
- [_____]

Discussion Topic 2: Batch Production Record Requirement

- Lilly ICOS proposes that batch records from a total of four manufactured primary stability batches, instead of all nine batches produced, are sufficient for meeting the needs of FDA field investigators and FDA headquarters reviewers; the four lots include two 5 mg batches, one 10 mg batch, and one 20 mg batch; one batch of each strength was used in the pharmacokinetic studies
- acceptable

Discussion Topic 3: Primary Stability Data for 20 mg Tablet

- Lilly ICOS proposes to provide, at the time of submission, ~~12~~ 6 months of primary stability data for the 5 mg and 10 mg tablets and 6 months of primary stability data for the 20 mg tablet; additional 20 mg tablet primary stability data for the 9 month and 12 month time points will be available during the review period; additional 24-month time points will be available during the review period for the 5 mg and 10 mg tablets
- acceptable; if the trend for the stability data from the 20 mg tablet strength is not comparable to the 5 mg and 10 mg tablets, a different expiry date for all three strength tablets or just the 20 mg tablet strength may result

Additional Topics

- Lilly ICOS stated that an established name for IC351 had been requested; a response from USAN is expected by the end of 2000
- Lilly ICOS stated that the earliest anticipated submission date for the NDA is June 2001

Decisions made:

- all proposals made by Lilly ICOS are acceptable

Action Items:

- minutes of this meeting will be provided to Lilly ICOS within 30 days

Minutes Preparer

Concurrence, Chair

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

/s/

Kim Colangelo
12/5/00 08:30:16 AM
CSO

Kim Colangelo
12/5/00 10:55:59 AM
CSO

Daniel A. Shames
12/6/00 04:04:52 PM
MEDICAL OFFICER

✓ Colangelo

Meeting Minutes

Date: August 30, 1999

Time: 10:30 AM-12:00 PM EDT

Location: Parklawn, Conference Room "C"

IND 54,553

Drug: IC351

Indication: erectile dysfunction

Sponsor:

Lilly ICOS LLC

Type of Meeting:

End of Phase 2

Meeting Chair:

Lisa Rarick, MD

External Lead:

Susan Sullivan

Meeting Recorder:

Kim Colangelo

FDA Attendees:

Lisa Rarick, MD – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Marianne Mann, MD – Deputy Director, DRUDP (HFD-580)

Mark Hirsch, MD - Medical Officer, DRUDP (HFD-580)

Brenda Gierhart, MD - Medical Officer, DRUDP (HFD-580)

Norman Marks, MD - Medical Officer, DRUDP (HFD-580)

Alex Jordan, PhD – Pharmacology/Toxicology Team Leader, DRUDP (HFD-580)

Jeri El-Hage, PhD – Pharmacology/Toxicology Reviewer, DRUDP (HFD-580)

Karen Davis-Bruno, PhD - Pharmacology/Toxicology Reviewer, DRUDP (HFD-580)

Ameeta Parekh, PhD - Clinical Pharmacology/Biopharmaceutics Team Leader, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)

Venkat Jarugula, PhD – Clinical Pharmacology/Biopharmaceutics Reviewer, DPE II @ DRUDP (HFD-580)

David Hoberman, PhD – Statistician, Division of Biometrics II (DOB II) @ DRUDP (HFD-580)

Terri Rumble, BSN – Chief, Project Management Staff, DRUDP (HFD-580)

Kim Colangelo, BS – Regulatory Project Manager, DRUDP (HFD-580)

Jeanine Best, MSN – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Greg Brophy, PhD – Regulatory

Jeffery Emmick, PhD, MD – Clinical Pharmacology

Kennerth Ferguson, PhD – Product Team CSO

Gary Higdon, BS – Regulatory

Pan-Yu Lai, PhD – Statistician

Malcom Mitchell, MB, BS, MFPM – Clinical Research

William Pullman, BMedSc, PhD, MD, FRACP – Medical Affairs

Peter Sausen, PhD – Toxicology

Susan Sullivan, BS – Regulatory

Steve Whitaker, MD – Clinical Research

Meeting Objective: To discuss and reach agreement on issues regarding Phase 3 trial design, submitted preclinical information, pharmacokinetic/pharmacodynamic (PK/PD) analysis, and safety; DRUDP contacted Lilly ICOS prior to the meeting to request that preclinical findings (see below) and clinical implications be discussed as the first topic on the agenda.

Background: IC351 is a phosphodiesterase Type 5 inhibitor being developed for the treatment of erectile dysfunction under IND 54,553; a preclinical safety report notifying DRUDP of non-reversible atrophy of the seminiferous tubules and vacuolization of the epithelium at doses of 60 mg/kg/day in dogs was received July 22, 1999; sperm counts also decreased at this dose; two Phase 1 studies are proposed to address this concern.

Discussion:

- clinical studies for sperm assessment:
 - the proposed clinical trials (LVCB and LVAU) are inadequate to assess potential damage to the tubules because sample collection is conducted too early to show effects following exposure of drug (days 4 (LVCB) or 10 (LVAU))
 - to assess potential damage to the seminiferous tubules, semen samples need to be collected at three and six months of daily dosing to analyze the next two generations of sperm
 - sperm assessments should include a measurement of concentration, motility and morphology (WHO recommendations)
 - a sub-group analysis can be incorporated in a Phase 3 trial to collect data on intermittent dosing, but daily dosing is needed to address the safety concern
 - recommend that the 6-month daily dosing safety study precede Phase 3 trials
 - recommend retaining the World Health Organization criteria in the ongoing trial, Protocol LVCB
 - the second acute Phase 1 study proposed (LVAU) is not needed but can be conducted at the sponsor's discretion
- the balance of the questions posed by Lilly ICOS are answered as if the safety issue discussed above was resolved
- Phase 3 trial design:
 - the proposed approach regarding dose selection is acceptable
 - the SEP is not considered validated, but the revisions proposed are acceptable for use in the Phase 3 trials
 - patients on short-acting nitrates will be excluded in Phase 3 trials (see attachment)
 - exclusion criteria of nitrate use in the previous 90 days is recommended; other proposals will be consulted to the Division of CardioRenal Drug Products (DCRDP)
 - issues regarding concomitant medications will be consulted to DCRDP
 - a single time limit for exclusion of patients with myocardial infarction, cardiac artery bypass graft (CABG) or angiography (i.e., 90 days) is recommended for simplicity of enrollment
 - collection of clinical QT interval data is being done for European regulatory authorities, not because of a potential safety issue

- endpoints of the EF domain, and SEP questions #2 and #3 are recommended; questions #3 and #4 of the IIEF are acceptable for exploratory purposes
- the full protocol for study LVBY (nitrate pharmacodynamic study, see attachment) has not been submitted for review; preliminary comment:
 - based on the information submitted, a positive result from this study may be supportive to remove a labeled contraindication for nitrates, while retaining a labeled warning or precaution statement; however, LVBY should be one component of an overall data package (including real use data) that will support removal of the nitrate contraindication
- inclusion of patients on nitrates in a planned stress-test protocol should be considered
- collection of pharmacokinetic data in diabetics at 20 mg is not planned, but was raised by DRUDP; data will be collected from geriatric and renal- and hepatic-impaired populations at 10 mg
- the _____ is not bioequivalent at the maximum plasma concentration (C_{max} ; the to-be-marketed formulation is 27% higher); 100 patients with one-year exposure must be at or above the expected exposure of the to-be-marketed dose and formulation; Lilly ICOS should also address any potential safety concerns related to C_{max}
- the information submitted to date does not support a priority review; justification for a priority review should be included with the NDA submission
- trials ongoing or initiated after February 2, 1999, need financial disclosure information; Lilly ICOS' proposal to comply with this rule is acceptable
- the rationale for waiver of pediatric studies is acceptable; Lilly ICOS should request a waiver in the NDA submission

Decisions made:

- the questions posed by Lilly ICOS are answered as if the safety issue discussed above was resolved:
 - Phase 3 trial comments:
 - the proposed approach regarding dose selection is acceptable
 - the SEP is not considered validated, but the revisions proposed are acceptable
 - patients on short-acting nitrates will be excluded
 - one-year exposures for safety need to be at exposures equivalent or above the marketed doses
 - the proposal for financial disclosure information is acceptable
 - a waiver for pediatric studies should be requested

Unresolved decisions:

- clinical program to address safety concerns with possible seminiferous tubule damage is pending review of a proposal from Lilly ICOS
- agreement on study LVBY (nitrate pharmacodynamic study) is pending review of the protocol

Action Items:

- Lilly ICOS should propose a safety study, along with justification for any variances from recommended design, timing, etc.; a Type A meeting will held if there are disagreements on the program
- Lilly ICOS will submit a full protocol of study LVBY for review
- minutes of this meeting will be provided to Lilly ICOS within 30 days

IND 54,553
Meeting Minutes 08.30.99
page 4

ATTACHMENT (sponsor overheads)

/S/
Minutes Preparer

/S/
Concurrence, Chair

cc:

Original IND 54,553

HFD-580/DivFile

HFD-580/Colangelo/Rumble/Rarick/Mann/Shames/Hirsch/Jordan/El-Hage/Rhee/Lin/Parekh

HFD-/Jarugula/Kammerman/Hoberman/Allen/Gierhart/Davis-Bruno

drafted: Colangelo, 09.20.99

concurrence: El-Hage, Mann, 09.20.99; Parekh, Hirsch, 09.21.99; Rarick, Rumble, 09.24.99

response not received: Jordan, Davis-Bruno, Jarugula, Hoberman

final: Colangelo, 09.29.99

MINUTES