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Jennifer L. Mercier
11/19/03 04:14:16 PM
CSO

MEMORANDUM

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

DATE: November 14, 2003

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

FROM: Office of Drug Safety, HFD-400
Division of Drug Risk Evaluation, HFD-430
Division of Surveillance, Research and Communication Support, HFD-410
Division of Medication Errors and Technical Support, HFD-420

SUBJECT: PID# D030380
Drug: Tadalafil (Cialis®), Lilly ICOS
NDA – 21-368
Topic: Risk Management Plan

EXECUTIVE SUMMARY:

The Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580, consulted Office of Drug Safety (ODS) to review and comment on a risk management plan (RMP) in support of the New Drug Application (NDA) for tadalafil (Cialis®, Lilly ICOS). This memorandum is in response to this consult.[1]

HFD-580 identified three areas of concern: a) The potential of tadalafil to interact with nitrates, some alpha-blockers, and alcohol. The concomitant use of tadalafil with any of these agents can potentiate their hypotensive effects; b) The potential of drug-drug interactions between tadalafil and cytochrome P4503A4 enzyme inhibitors such as ketoconazole, erythromycin, clarithromycin, itraconazole, grapefruit juice, and some protease inhibitors, such as ritonavir, and saquinavir. Co-administration of tadalafil with CYP4503A4 inhibitors may increase the plasma concentrations of tadalafil and consequently has the potential to increase the incidence of undesirable effects; c) The potential of concomitant administration of CYP3A4 inducers such as

1 The Division of Surveillance, Research, and Communication Support (DSRCS) completed a review of the proposed Patient Package Insert (PPI) on tadalafil on August 15, 2003. This review contains input from the Division of Drug Risk Evaluation (DDRE), DSRCS, and Division of Medication Errors and Technical Support (DMETS). Jeanine Best addresses the proposed educational program, Dr. Judy Staffa addresses issues related to proposed postmarketing surveillance studies, Carol Holquist addresses issues related to the prevention of medication errors, Paula Gish summarizes concerns expressed by HFD-580, and Dr. Ahmad evaluates the remainder of the document.

rifampicin, phenobarbital, phenytoin and carbamazepine to decrease plasma concentrations of tadalafil.

Tadalafil is already approved in certain other countries[2] with broader contraindications including certain serious cardiac conditions and recent stroke. The current labeling proposed by the sponsor in the U.S. does not specifically contraindicate these conditions but only includes these in the warning section. Consideration should be given to revise the proposed labeling of tadalafil to include these additional categories of patients in the contraindication section as well.

While data on repetitive daily dosing in normal volunteers (100 mg q 21 days per report) have not demonstrated clinically significant hypotensive effects, there is a potential that blood level increases and drug interactions experienced by the broad population of users after approval may lead to clinically significant adverse events related to reduced blood pressure in some patients.

Other concerns of ODS include limited data on the safety of tadalafil in patients with severe renal insufficiency and severe hepatic insufficiency; risk of priapism; lack of data on the safety and efficacy of tadalafil when used concomitantly with certain antihypertensives and other drugs for ED.

The sponsor has proposed a number of risk management tools to address certain risks that have been identified with tadalafil. The primary goal of the sponsor-submitted RMP is to decrease the concomitant use of tadalafil with nitrates. Additional goals of the sponsor are to decrease the potential risk associated with tadalafil use in (a) patients taking alpha blockers, (b) patients taking combinations of multiple antihypertensive agents, and (c) patients consuming ethanol (alcohol) to the level of intoxication. The final goal of the RMP is to educate patients that tadalafil does not protect against sexually transmitted diseases.

The risk management tools proposed by the sponsor include labeling, a call center (to answer questions pertaining to information, adverse events, or product complaints), and standard safety surveillance. While the sponsor has listed several goals of RMP, in its educational intervention directed towards health care professionals and patients, the emphasis is only on one, i.e., contraindication of tadalafil with nitrates. [redacted] However, no details are included precluding a thorough assessment and evaluation of these studies. The RMP indicates that these studies will be conducted as a part of the sponsor's previously agreed-upon post-marketing commitments to the European Medicines Evaluation Agency (EMEA).

The proposed RMP has significant gaps and needs to be revised in light of the recommendations outlined in the following section in an attempt to manage the currently known risks and concerns with the use of tadalafil.

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2 Including Australia, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, and United Kingdom.

11 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Toni Piazza-Hepp, Pharm. D., Acting Director, DSRCS, HFD-410, ODS

Jerry Phillips, R.Ph., Acting Director, DMETS, HFD-420, ODS

Anne Trontell, M.D., M.P.H., Deputy Director, HFD-400, ODS

Authors - ODS Review Team:
Syed Rizwanuddin Ahmad, M.D., M.P.H, Medical Epidemiologist, DDRE
Paula Gish, R.Ph., Safety Evaluator, DDRE
Judy A. Staffa, Ph.D.,R.Ph., Epidemiology Team Leader, DSRCS
Jeanine Best, M.S.N., R.N., P.N.P., Patient Product Information Specialist, DSRCS
Carol Holquist, R.Ph., Deputy Director, DMETS

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/s/

Mary Dempsey
11/14/03 10:14:22 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
11/14/03 12:06:17 PM
DRUG SAFETY OFFICE REVIEWER

Leslie Wheelock
11/14/03 12:12:01 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Toni Piazza Hepp, Pharm.D.

Carol Holquist
11/14/03 12:28:51 PM
DRUG SAFETY OFFICE REVIEWER

Anne Trontell
11/14/03 12:34:29 PM
DRUG SAFETY OFFICE REVIEWER

ADMINISTRATIVE REVIEW OF NDA (review pkg)
OFFICE OF DRUG EVALUATION III

NDA: 21-368
Drug: Cialis (tadalafil) tablets
Classification: 1 S
Sponsor: Lilly Icos
Project Manager/CSO: Freshnie DeGuia

Reviewer: Bronwyn Collier, ADRA ODE III
Review Date: November 14, 2003

Review Cycle 1
Date Submitted: June 28, 2001
Date Received: June 29, 2001
Action: Approvable April 29, 2002

Review Cycle 2
Date Resubmitted: may 27, 2003
Date Received: May 28, 2003
Goal Date: November 28, 2003
Proposed Action: approval

	STATUS	COMMENTS
ACTION LETTER	draft	
EXCLUSIVITY CHECKLIST	draft	
DEBARMENT STATEMENT	verified	
PEDIATRIC PAGE	final	
DSI AUDITS	completed 1st review cycle	
FACILITY INSPECTIONS	pending	overall recommendation pending

REVIEWS	STATUS	COMMENTS
SUMMARY REVIEWS	pending	
TRADE NAME & LABELING REVIEWS	final	Trade name acceptable. Final labeling negotiations ongoing.
CLINICAL	draft	
SAFETY UPDATE	draft	included in clinical review
FINANCIAL DISCLOSURE	completed 1st	

	review cycle	
STATISTICAL	final	
BIOPHARM	draft	
CMC	draft	
EA	completed 1st review cycle	
MICRO (validation of sterilization)	N/A	
STABILITY (stats)	completed 1st review cycle	
PHARM/TOX	draft	
CAC (stats)	completed 1st review cycle	
CAC/ECAC REPORT	completed 1st review cycle	
CONSULTS	final	ophthalmology cardiorenal

Labeling: negotiations with sponsor ongoing
Phase 4 Commitments: Discussions ongoing at time of review.
Advisory Committee Meeting: none

Comments: Prior to an action, documents in draft must be finalized.

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/s/

Bronwyn Collier
11/20/03 08:13:40 AM
CSO

MEMO

45 Day Filing Meeting Checklist
Project Management

NDA 21-368
Cialis
20 mg

ITEM	YES	NO	COMMENT
1) Do any of the following apply to this application (i.e., if yes, the application **MUST BE REFUSED TO FILE** under 314.100(e) and there is no filing over protest):			
a. Is the drug product already covered by an approved application?		X	
b. Does the submission purport to be an abbreviated application under 314.55; however, the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.559b)?		X	
c. Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?		X	
2) Do any of the following apply to this application (i.e., if NO, the application **MAY BE REFUSED TO FILE** under 314.100(d) and there is the potential for filing over protest):			
a. Does the application contain a completed application form as required under 314.50 or 314.55?	X		

b. On its face, does the application contain the sections of an application required by regulation and Center guidelines?	X		

ITEM	YES	NO	COMMENT
c. Has the applicant submitted a complete environmental assessment, which addresses each of the items, specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under 25.24 of the CFR?	X		
d. On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?	X		Electronic submissions acceptable following Guidance for electronic submissions
e. Is the NDA indexed and paginated?	X		
f. On its face, is the NDA legible?	X		
g. Has the applicant submitted all required copies of the submission and various sections of the submission?	X		
h. Has the sponsor submitted all special Studies/data requested by the Division during presubmission Discussion with the sponsor?	X		

i. Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?	X		
j. If required, has the applicant submitted carcinogenicity studies?	X		
ITEM	**YES**	**NO**	**COMMENT**
k. On its face, does the application contain at least two adequate and well-controlled clinical trials?	X		
l. Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	X		
m. Have all articles/study reports been submitted either in English or translated into English?	X		
n. Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?	X		
3) From a project management perspective, is this NDA fileable? If "no", please state why it is not.	X		

Regulatory Project Manager

cc:
Original NDA
HFD-580/DivFile
HFD-580/PM/

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/s/

Dornette Spell-LeSane
3/25/02 12:46:15 PM
CSO

MEMORANDUM

Date: 12 November 2003
From: Suzanne R. Thornton, Ph.D.
Acting Supervisory Pharmacologist, HFD-580
To: File for NDA #21-368, N000AZ
Re: Approvability for Pharmacology and Toxicology
Cialis (tadalafil)

Tadalafil is a PDE5 inhibitor for the indication of erectile dysfunction in men. The submission is a complete response to an approvable letter. As stated in the original review cycle, Dr. Shin continues to believe that a potential for immune mediated hypersensitivity arteritis is possible in humans.

Dr. Shin's evidence, with some speculation, is based on non-clinical observations and literature articles. In 1-month and 6-month dog studies conducted by the Sponsor an increased incidence of disseminated arteritis was observed at unbound tadalafil exposure of 1- to 54-fold above the human exposure (AUC) at the MRHD of 20 mg. In a 12-month dog study using a different supplier, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound tadalafil exposures of approximately 14- to 18-fold the human exposure at the MRHD of 20 mg. It should be noted that no evidence of immune mediated hypersensitivity arteritis has been found in the human clinical trials where the Sponsor did examine potential inflammatory biomarkers.

Unfortunately there is no current resolution to address Dr. Shin's concerns as no additional non-clinical data will provide information on human relevance and probability of the immune mediated hypersensitivity arteritis.

Following the review of the original submission, the Associate Director for Pharmacology/Toxicology for ODE III, Dr. Leighton, concurred with 'the Division's analysis (that the arteritis information be included in the label) but recommended that the Division seek the opinion of the Pharmacology/Toxicology Coordinating Committee (PTCC) or appropriate subcommittee to ensure consistent labeling of these findings.' This issue was not presented to PTCC, but was presented to the PTCC Arteritis Working Group during the current review cycle, however, no discussion or decision on the inclusion of the information in label occurred. Dr. Shin and I feel that the data based information on vascular inflammation from the Sponsor's non-clinical studies should be included in the label because tadalafil is significantly different from other approved PDE5 inhibitors in that it has a longer half-life, lower exposure multiples, possible metabolite activity, produces a different mode of arteritis (involves organs other than the heart), and has higher selectivity and inhibition of PDE11. The most concerning difference between tadalafil and other PDE5 inhibitors is its selective inhibition of PDE 11. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1, an enzyme found in

human skeletal muscle.

Regardless of Dr. Shin's concerns, she and I support her previous recommendation of 'approval' for the NDA. Appropriate labeling revisions including the addition of PDE11 information and the addition of an 'Animal Toxicology' section detailing the non-clinical arteritis findings have been included and accepted by the Sponsor.

Recommendations: The pharmacology and toxicology data supports approval of this NDA. There are no outstanding issues.

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/s/

Suzanne Thornton
11/12/03 05:19:45 PM
PHARMACOLOGIST

Addendum to Review

NDA: 21-368
Submission date: 4/16/03, 5/27/03
Drug name: IC351, Cialis, Tadalafil
Sponsor: Lilly ICOS LLC
Division: DRUDP, HFD-580
Reviewer: Yangmee Shin

Review of Complete Response & Pharmacology Amendment

NDA 21-368 got an approvable action on 4/29/02 pending receipt of information on deficiencies including analysis of reports of myalgia and back pain for assessment of vasculitis and any direct effect of Cialis or the methylcatechol glucuronide metabolite. In addition, the Division asked the sponsor to evaluate possible drug-related immune-mediated effects using biomarkers such as antineutrophil cytoplasmic antibodies (ANCA) from serum samples, if available, to rule out hypersensitivity vasculitis caused by treatment-related myalgia. This complete response includes retrospective and prospective analysis of back pain/myalgia, and additional pharmacology studies of IC351 on the inhibition of human PDE11A1 and hERG channel activity.

PHARMACOLOGY

Study Title: Inhibition of Human PDE11A1 Activity by IC351 and its Metabolites (#02-0013-11)

Methods: PDE assays were performed by using cAMP or cGMP as substrates in the absence and presence of IC351, methylcatechol (IC710), catechol (IC711) or methylcatechol glucuronide (LY559171) dissolved in 100% DMSO.

Results: IC_{50} values of PDE5A1 for IC351, methylcatechol, catechol and methylcatechol glucuronide were [redacted], respectively. The values were similar to those reported in previous study reports with the exception of PDE5A1 for methylcatechol glucuronide (14 μM). The sponsor stated that the difference could be the buffer and the pH in the assays. IC_{50} values of PDE11A1 for IC351, methylcatechol, catechol and methylcatechol glucuronide using cGMP as a substrate were [redacted] respectively, which was comparable to previous values using cAMP as a substrate. Table below summarizes the IC_{50} values and selectivity ratios utilizing cGMP as a substrate.

Inhibition of Human PDE 5A1 & 11A1 by IC351 and its Metabolites

Compound	PDE#	IC_{50} (μM)	Selectivity Ratio (PDE11A1/PDE5A1)
Cialis	5A1	[redacted]	
	11A1		14
Methylcatechol	5A1	[redacted]	
	11A1		6
Catechol	5A1	[redacted]	
	11A1		5
Methylcatechol glucuronide	5A1	[redacted]	
	11A1		3.6

#PDE5A1=human recombinant expressed in *Saccharomyces cerevisiae* & purified from baculovirus infected Sf9 cell extracts
PDE11A1= human recombinant expressed as a His tagged protein & partially purified from baculovirus infected Sf9 cell extracts

Summary/Conclusion: IC351 and its metabolites had low selectivity ratios of PDE11A1 *vs* PDE5A1 from 3.6 to 14 fold, indicating that the compounds are highly specific for PDE11A1. Based on C_{max} (514 ng/mL, 1320 nM) at the MRHD of 20 mg, Cialis and/or its catechol metabolite may alter the activity of PDE11A1 at its therapeutic doses.

SAFETY PHARMACOLOGY

Study Title: hERG Blocking Profile of Cialis (#LLY02_01), Levitra and Viagra

Methods: Human cardiac I_{K_r} currents of E-4031 (100 nM) as a positive control, IC351, vardenafil and sildenafil at 0.1, 0.3, 1, 3, 10 and 100 μM (in DMSO) were recorded from stably expressed HEK 293 cells by a voltage pulse to +10 mV (500 msec) from a holding potential of −75 mV and repolarization to -40 mV with a pulse frequency of 0.1 Hz at 4 mM extracellular K^+ concentration. Rate-dependent effects were determined by a train of 20 depolarizing voltage steps at 1, 2 and 3 Hz at −75 mV with 100 μM of drugs.

Results: Cialis, Levitra and Viagra dose-dependently reduced hERG current amplitude with IC_{50} (μM) values of 100 (estimated), 12.8 and 33.3, respectively, with no rate-dependent block of hERG over the range of 1 to 3 Hz at 100 μM. However, accurate dose-response relationship of Cialis could not be determined since 50% inhibition was achieved at the highest concentration tested. The sponsor stated that concentrations higher than 100 μM could not be evaluated due to the compound's solubility limit in the perfusion solution.

IC_{50} of hERG Activity by Cialis, Levitra and Viagra

Compound	IC_{50} (μM)
Cialis	100 (estimated)
Levitra	12.8
Viagra	33.3

Summary/Conclusions: C_{max} of the unbound drug (31 ng/mL, 79 nM) at the MRHD of 20 mg corresponded to approximately 127 fold above the IC_{50} (100 μM) of hERG blockade, indicating that the drug has a weak potential of QT prolongation risk.

COMPLETE RESPONSE TO BACK PAIN AND MYALGIA EVENTS

Introduction: Myalgia and back pain symptoms observed in Cialis-treated patients were frequently described as bilateral, diffuse, deep muscle discomfort and lower lumbar and/or gluteal and/or posterior thigh pain as opposed to localization to the area of the kidneys (flank pain). The pain was often noted in the recumbent position or exacerbated by recumbency, and often relieved with ambulation. One severe case was observed in an elderly man taking 20 mg on 3 occasions of bilateral leg pain associated with difficulty in urinating/defacating, and resolved in 50-60 hrs post-dosing. There were no clinically significant changes of erythrocyte sedimentation rate (ESR) and creatinine phophokinase (CPK) measured in ED patients with symptoms treated with 2, 5, 10 or 25 mg (14 doses for 21 days) in a Phase II study (#LVBF).

Preclinical studies: Treatment–related vasculitis was observed in mice, rats and dogs at unbound drug exposures of 1-54 fold the human exposure at a clinical dose of 20 mg. Unlike the classic vasodilator-induced vasculitis observed with other PDE5 inhibitors (Viagra, Levitra), in which the lesions were mostly confined to the coronary arteries in dogs, Cialis produced disseminated arteritis in the absence of hemodynamic changes. In a 1-year dog study (different colony), the disseminated arteritis was not observed, but there were 2 dogs with marked thrombocytopenia and neutropenia with inflammatory signs (1 dog with left coronary artery perivasculitis) at 14-18 fold the human exposures. The abnormal blood-cell findings were reversible within 2 weeks upon removal of the drug (see original NDA review).

Retrospective clinical analysis: In clinical pharmacology studies, the incidence of myalgia and back pain was mostly mild to moderate, and dose-related (12.5, 11.3, 18.2, 28.7 & 77.8% at 2.5, 5, 10, 20 & 100 mg, respectively) compared to 4.2% in placebo and 6.8% in sildenafil-treated subjects. The incidence of pooled events in clinical studies ranged from 6.8-16.4% in Cialis-treated subjects (up to 20 mg) compared to 3.7-4.8% in placebo-treated subjects. Myalgia and back pain were reported more frequently in subjects

receiving Cialis than in subjects receiving other PDE5 inhibitors (Viagra, Levitra) at therapeutic doses. Overall discontinuation rate due to myalgia and back pain was <1%. Most of the concomitant pain medications administered were NSAIDs or acetaminophen, and there was low frequency of use of muscle relaxants and narcotics. The onset of the symptoms typically occurred 12 to 24 hours postdose, and resolved within 48 hours in most subjects. Daily dosing of 10 and 20 mg for 6 months decreased the prevalence of myalgia and back pain (#LVCD, #LVCZ). However, this could be due to increased tolerance to the long-acting PDE5 inhibitor. There was a tendency to increase the events with increasing age.

Prospective clinical analysis: The sponsor conducted an algorithm of laboratory assessments including inflammatory markers of ESR, CPK, serum amyloid A (SAA) and C-reactive protein (CRP) in ED patients with myalgia and back pain (n=153). Neither clinically significant changes in inflammatory parameters (ESR, creatinine) nor signs (rash, pyrexia or hematuria) suggestive of vasculitis or immune disease were observed in laboratory analyses. There were no significant differences in effective renal plasma flow and renal function in healthy young males with myalgia and back pain using radiographic techniques (3/9 at 20 mg, 3/8 at 80 mg, #LVFA). To rule out the possibility of the methylcatechol glucuronide metabolite associated with myalgia and back pain, the sponsor coadministered Cialis with a CYP3A4 inhibitor in healthy subjects (#LVEV). The myalgia and back pain incidence was not markedly different between the coadministration of Cialis and ritonavir (50%, 14/28) and Cialis alone (37.5%, 3/8) despite the reduced exposure to the metabolite when Cialis was coadministered with ritonavir. In renally insufficient subjects (#LVDT), no myalgia and back pain were reported following a single dose of 5 (n=6), 10 (n=12) or 20 mg (n=6) in male and female subjects with end-stage renal disease before hemodialysis despite a 3 fold higher exposure to the methylcatechol glucuronide than in healthy subjects. The sponsor concluded that the myalgia and back pain are not related to a serious underlying pathology associated with the rhabdomyolysis, myopathy, vasculitis, eosinophilia-myalgia syndrome or renal function abnormalities, and are neither associated with an ANCA-positive vasculitis nor due to methylcatechol glucuronide metabolite. It should be noted that the results are different from the previous results in the renally impaired patients with an increased incidence of myalgia and back pain. The reason for the discrepancy is not explained.

Sponsor's response on the Division's recommendation of ANCA test: At a teleconference on 3/19/03, the Division (upon the Pharm/Tox reviewer's recommendation) asked the sponsor to evaluate ANCA from the serum samples of patients who underwent the algorithm or from patients in ongoing studies, if available, to rule out immune-mediated vasculitis. The sponsor responded that there were neither stored nor well-suited serums in ongoing studies for the test, and provided the following information regarding the utility of ANCA test.

Sponsor: The clinical experience with Cialis does not suggest an association with a clinical syndrome that fulfills the American College of Rheumatology's classification of hypersensitivity (drug-induced) vasculitis.

Reviewer's comment: A definitive classification of the vascular syndrome is difficult because of the complicated diagnosis of the condition which can be due to many factors. These factors include inappropriate diagnosis by the physicians, variable time course for agents and patients for vasculitis development after initiating drug therapy, lack of confirmatory data regarding drug rechallenge, failure to evaluate appropriate laboratory and invasive tests, and failure to use standardized general terminology (Ann. Pharmacother. 36: 130, 2002). In addition, the pathogenesis of human vasculitides is still poorly understood. Many drugs can provoke a range of symptoms indicative of more than one mechanism. The actual clinical manifestations of a reaction can vary between patients. The sponsor's information was based on the ACR classification of vasculitides proposed in 1990 (Arthritis and Rheumatism 33: 1065). The criteria were based on the analysis of 807 patients with definitive vasculitis to discriminate between patients who had different forms of systemic vasculitis, but do not differentiate patients with vasculitis

from those without. Since then, new criteria for differentiating specifically hypersensitivity from other vasculitides have been proposed.

Sponsor: *Treatment-emergent signs and symptoms experienced by tadalafil subjects with back pain or myalgia are similarly inconsistent with vasculitis.*

Reviewer's comment: Although specific events associated with hypersensitivity vasculitis such as purpura, rash, hematuria or inflammation of the upper respiratory tract, *etc* fulfilling the ACR criteria for the diagnosis have not been observed in subjects exposed to Cialis possibly up to a year at the MRHD, myalgia could be an initial presenting symptom. Duration of therapy before such vasculitic lesions was extremely variable ranging from hours to years. For example, hydralazine-induced cutaneous vasculitic manifestations of palpable purpuric and maculopapular eruptions, hemorrhagic blisters, nasal septum, *etc* proceeded by the initial symptoms of arthralgias and myalgias, have occurred 6 months to 13 years after initiating treatment (Br. Med. J. 280: 156, 1980). In addition, a catechol moiety of the Cialis metabolites may act as an immunogenic epitope of drug-hapten formation for drug-induced hypersensitivity vasculitis. Cialis is metabolized to catechol, methylcatechol and then methylcatechol glucuronide. Hypersensitivity reactions, for example, of methyldopa or levodopa are thought to be caused by the catechol moiety of the drugs (Immunopharm. Immunotoxicol. 15: 621, 1993). With Cialis, the onset of these events generally occurred within 12-24 hrs after the administration of Cialis, which were similar to the T_{max} of the methylcatechol glucuronide. In renally impaired patients (from previous results), there was an increased incidence (2-4 fold) of myalgia/back pain with prolonged half-life (~55 hrs) of methylcatechol glucuronide. As indicated by the Medical Reviewer in the NDA review, this may present an unknown safety risk and may be due to the long sojourn of the drug in the body and the associated increased exposure to the metabolite.

Sponsor: *Immunosuppressive and cytotoxic agents were not administered to tadalafil subjects experiencing back pain or myalgia. This suggests that a progressive rheumatic syndrome with high systemic morbidity was not present in those subjects.*

Reviewer's comment: Drug-induced vasculitis can range from cutaneous and mild systemic symptoms to invasive involvement of several organs. In the majority of cases, vasculitis resolves after discontinuing the drug. Patients with more severe, often life-threatening, manifestations have required treatment with corticosteroids, plasmapheresis, hemodialysis or cyclophophamide.

Sponsor: *Sensitive laboratory and radiographic markers of inflammation failed to reveal any signal of an inflammatory response in tadalafil subjects with back pain or myalgia.*

Reviewer's comment: The markers tested are acute phase responders for general inflammation, especially for deep bed inflammation. These markers are sensitive but not specific, and are strong predictors of cardiovascular risk of future myocardial infarction and stroke (Circulation 107: 499, 2003). Positive ANCA titers were also found in patients with peripheral vascular disease in the absence of positive serum markers (CRP, SAA) of inflammation (J. Intern. Med. 251: 29, 2002). In addition, as the sponsor indicated, the radiographic techniques may not be sufficiently sensitive to detect moderate changes in pooling of venous blood in the large muscle groups of the lower back and gluteal region.

Sponsor: *Tests for ANCA should be reserved for suspected cases of Wegener's granulomatosis and undiagnosed glomerulopathy, as these tests have high false positive rates in a low risk population such as the tadalafil clinical trial population.*

Reviewer's comment: Many drug-induced vasculitis cases are possible manifestations of immune complex disease, and ANCAs have been extensively used for the diagnosis. Patients presenting cutaneous, GI, hepatic, pulmonary vasculitis as well as renal manifestations demonstrated positive ANCA

titers (Ann Pharmacother 36: 130, 2002). ANCAs are highly specific in Wegner's granulomatosis and microscopic polyangiitis. However, ANCAs were already detectable in most cases in the sera with early nonspecific signs like arthralgia, fatigue and fever or localized symptoms such as sinusitis and cough (Clev. Clin. J. Med. 69: 100, 2002).

Sponsor: Given the absence of a change in the tests for inflammation that were prospectively conducted and the limitations of the ANCA test, performing such an analysis will not add useful additional information regarding the nature of back pain or myalgia occurring in patients receiving tadalafil.

Reviewer's comment: Recent studies suggest that ANCAs are involved in many steps of an inflammatory process with other mediators of diseases (Kidney Int. 59: 1981, 2001). Because ANCAs are already present in early stages of vasculitis and non-vasculitic diseases, their testing may increase a probability of an early and correct diagnosis, and may contribute to the prognosis of patients (Clin. Immunol. 106: 73, 2003).

Vasocongestion hypothesis: The sponsor stated that the myalgia and back pain are not related to a serious underlying pathology associated with the rhabdomyolysis, myopathy, vasculitis, eosinophilia-myalgia syndrome and renal function abnormalities, and are highly unlikely associated with an ANCA-positive vasculitis. The sponsor further stated that PDE5 is present in the skeletal muscle tissue, and the inhibition of PDE5 in the muscles of the back could result in vasodilatation in those muscles with an accompanying increased blood flow or vascular congestion and with back pain occurring particularly during recumbency and being relieved by activity. The hypothesis on drug-induced vasocongestion in the skeletal muscle was based on studies involving administration of diuretics and a hemodialysis program. In a study (#LVAP) with 10 mg Cialis and theophylline for 7 consecutive dosing in healthy male patients (n=18), subjects treated with Cialis alone, theophylline plus Cialis, theophylline and placebo reported back pain with 58.8, 6.7, 13.3 and 6.3%, and myalgia with 17.6, 6.7, 6.7 and 0%, respectively, despite no effect the plasma levels of Cialis with coadministration of theophylline. In another study where subjects were on hemodialysis (#LVAJ), no patients with renal impairment developed myalgia and back pain administered with Cialis. The sponsor stated that hemodialysis may decrease extracellular fluid volume similar to a diuretic effect, thereby decreasing a potential effect of Cialis on vasocongestion and protecting against the development of myalgia and back pain.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The etiology and/or mechanism of myalgia and back pain observed in humans associated with Cialis are not clearly understood. Available data in 153 subjects who reported myalgia and back pain did not show evidence of inflammation (ESR, CRP and SAA), of muscle damage or rhabdomyolysis (CPK, aldolase, AST, urine Hb) or of eosinophilia. The sponsor hypothesized that the development of myalgia and back pain is a class effect of PDE5 inhibition secondary to vasocongestion in the lower lumbar and gluteal musculature, and not associated with an immune-mediated hypersensitivity vasculitis in the absence of cutaneous, pulmonary, or renal failure. However, the information provided is not sufficient to conclude that myalgia and back pain are a class effect of PDE5 inhibitors due to following reasons: 1) limited information on preclinical/clinical findings is available because of poor understanding of pathogenesis to assess risks to humans; 2) there is a lack of valid markers for nonclinical and clinical monitoring; 3) Cialis is different from sildenafil and vardenafil with a distinct chemical structure and a longer duration of action; 4) Cialis is metabolized to catechol, methylcatechol and then to methylcatechol glucuronide, which possess a catechol moiety responsible for certain drug-induced hypersensitivity (Immunopharm. Immunotoxicol. 15: 621, 1993); and 5) Cialis and/or its catechol metabolite possess unknown physiological roles due to PDE11A1 inhibition within therapeutic range with a 5-14 fold selectivity (PDE11A1 *vs* PDE5A1) compared to Viagra and Levitra with a >300-fold selectivity.

Unresolved pharmacology/toxicology issues: Dose-related symptoms of myalgia and back pain in Cialis-treated subjects have unknown etiology and/or mechanism (see previous NDA review and above). The low selectivity of Cialis and/or its catechol metabolite (5-14 fold) on PDE11A1 *vs* PDE5A1 is another concern since the PDE11A1 inhibition (IC_{50}=15 nM for Cialis, 170 nM for catechol metabolite) occurs at clinical doses (C_{max}=514 ng/mL, 1320 nM at the MRHD of 20 mg). PDE11A is expressed in skeletal muscle, liver, testes, kidney, pituitary, thyroid, and salivary gland. Particularly, PDE11A1 is mainly found in human skeletal muscle. PDE11A gene is known to undergo tissue-specific alternative splicing that generates structurally distinct splice variants expressed in a tissue-specific manner, suggesting their specific physiological roles in the tissues (J. Biol. Chem. 275: 31469, 2000; Eur. J. Biochem. 268:168, 2001). Although the physiological significance and its clinical consequences of PDE11A1 inhibition have not been elucidated, the inhibition of Cialis and/or its catechol metabolite on PDE11A1 at therapeutic doses could lead to an increase in certain adverse effects such as musculoskeletal disorders.

Recommendation: From Pharm/Tox perspective, non-clinical studies conducted support the approval for Cialis. However, it would be reasonable to include some information on animal findings in the label due to insufficient information provided to conclude the sponsor's hypothesis and unidentified differences in animal findings with tadalafil compared to sildenafil and vardenafil.

Suggested labeling Under Animal Toxicology: (b)(4) [redacted] (b)(4) [redacted] (b)(4) [redacted] In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound tadalafil exposure of 2- to 33-fold above the human exposures (AUCs) at the MRHD of 20 mg. In dogs, disseminated arteritis (b)(4) [redacted] in 1- and 6-month studies at unbound tadalafil exposure of 1- to 54-fold above the human exposure (AUC) at the MRHD of 20 mg. (b)(4) [redacted] (b)(4) [redacted] in a 12-month study at unbound tadalafil exposures of approximately 14-18 fold the human exposure at the MRHD of 20 mg.

Reviewer Signature _____

Supervisor Signature_____ **Concurrence Yes** ___ **No** ___

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/s/

Yangmee Shin
11/13/03 09:34:16 AM
PHARMACOLOGIST

Suzanne Thornton
11/13/03 09:41:57 AM
PHARMACOLOGIST

4 page(s) of revised draft labeling has been redacted from this portion of the review.

Office of Drug Safety

MEMO

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

From: Marci Lee, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Eufrecina DeGuia
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

Date: September 24, 2003

Re: ODS Consult 00-0120-4; Cialis (Tadalafil) Tablets; NDA 21-368

This memorandum is in response to a July 1, 2003 request from your Division for a final review of the proprietary name, Cialis. In October 2000, DMETS conducted the initial proprietary name review for Cialis. Subsequently, DMETS re-reviewed Cialis in January 2002 and again in February 2002. The labels and labeling were reviewed in January 2002 and April 2002. The proposed risk management program for Cialis is currently under review.

DMETS' Phonetic Orthographic Computer Analysis (POCA) database was unavailable to search at the time of this review. However, DMETS has not identified any additional marketed proprietary or established names that have the potential for confusion with Cialis since we conducted our last proprietary name review dated February 19, 2002 (ODS consult 00-0120-1). [redacted] Since Claritin is now available without a prescription and Cialis will rarely be used in an inpatient setting, the likelihood for confusion between Claritin and Cialis is minimized.

The Division of Medication Errors and Technical Support (DMETS) reviewed revised container labels from the September 11, 2003 submission and the insert labeling including the "Information for the Patient" section from the June 5, 2003 submission.

In addition, there are several recommendations from previous reviews that have not been implemented by the sponsor. These recommendations, along with the recommendations for the revised labels and labeling are listed on page two.

LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft container labels and insert labeling for Cialis, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, in the interest of minimizing potential user error.

A. CONTAINER LABEL (30 tablets – 10 mg and 20 mg)

1. The statement "See accompanying literature for dosage" should be revised to state "Usual dosage: See accompanying literature for dosage ".

2. The statement " No. 4464" should be relocated to the side panel or deleted.

3. We recommend the use of a child resistant cap since the product is stored in a unit of use bottle.

B. INSERT LABELING (10 mg and 20 mg)

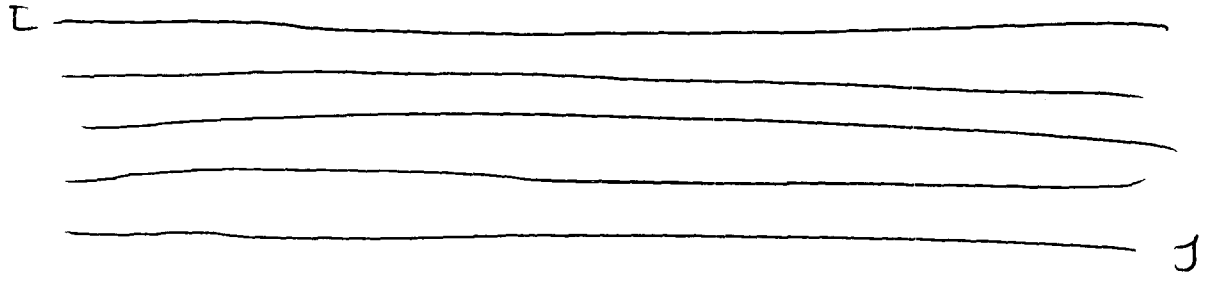
PRECAUTIONS, Drug Interactions subsection

The important safety information is presented in a narrative format that is difficult to read. Revise the format of this information to make it clearer. Consider use of a table, shading and font variations to clarify this section.

C. INFORMATION FOR THE PATIENT (10 mg and 20 mg)

DMETS notes that the Division of Surveillance, Research, and Communication Support (DSRCS) is currently reviewing the 'Information For The Patient' labeling. However, DMETS notes the following comments.

1. The following statements convey important information about Cialis. Consider including this information in a section entitled "What is the most important information I should know about Cialis?"



2. Increase the prominence of the statement: "Do not share your medicine with anyone else." That is located in the General Information Section.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) had no concerns from a promotional perspective during the initial or final review of the name, Cialis.

The Division of Medication Errors and Technical Support (DMETS) considers this a final name 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 project manager, Sammie Beam at 301-827-3242.

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/s/

Marci Ann Lee
9/25/03 11:59:58 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/26/03 04:16:39 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-368
Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cialis (tadalafil).

We also refer to your May 27, 2003 Complete Response to our April 29, 2002 approvable letter.

We are currently reviewing the Clinical Pharmacology and Biopharmaceutics section of your application and determined that we need more information/supplemental data regarding the datasets submitted in support of the following two studies:

> *Study H6D-EW-LVFB:* An Investigator- and Subject-Blind, Placebo-Controlled Study to Assess the Electrophysiologic Effect of 100 mg IC351 or Placebo on QT Interval with Ibutilide as an Open-Label Positive Control in Healthy Male Subjects
>
> *Study H6D-EW-LVDT:* A Study to Investigate the Tolerability and Pharmacokinetics of IC351 in Subjects on Hemodialysis for Renal Failure

1. Please provide a complete description of the columns of data in the each of the electronic datasets submitted in support of Study LVFB and Study LVDT. That is, provide a description of each possible value of each column variable and the units of each measurement. When doing so, explain blank values in the datasets.

   a) For example, in the ECG.XPT dataset submitted with Study H6D-EW-LVFB, four different values for PERIOD exist (PERIOD=1,2,3,99), but it is unclear what each of these values corresponds to. These PERIOD values were not defined in the "define.pdf" file that defined the columns in the data set. Please clarify what (if any) regimen (e.g. tadalafil, placebo, ibutilide) or portion of the study (e.g. pre-dose, post-dose, other?) the values indicate.

   b) In the BIOP.XPT dataset submitted with Study H6D-EW-LVDT, there are numerous blanks in the NTIME column. Please explain whether the blanks represent missing data, some standard value (e.g. last value carried forward), and/or something else.

2. Provide the following information regarding the ECG.xpt, ECG2.xpt, ECGIV.xpt, and ECGX.xpt datasets submitted in support of Study LVFB:

a) Append a column to each dataset listing the treatment (e.g. placebo, tadalafil, ibutilide) corresponding to each line of data.

b) Append a column of RR values corresponding to measured QT values for each line of data.

c) Append 3 columns to each of the 4 datasets (ECG.xpt, ECG2.xpt, ECGIV.xpt, and ECGX.xpt) listing: (1) the dose of drug, (2) the duration of infusion (NA or a flag variable for oral formulations), and (3) drug concentration.

d) Append a column to the datasets listing DATE in standard calendar format.

In addition, follow the above guidelines when submitting the data from the ibutilide dose-finding study (for Study LVFB).

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
8/22/03 10:04:36 AM

MEMORANDUM

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

DATE: August 15, 2003

TO: Dan Shames, M.D. Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Eufrecina DeGuia, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Cialis (tadalafil) tablets, NDA 21-368

Summary

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Cialis (tadalafil) tablets, NDA 21-368. It has been reviewed by our office and DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on May 27, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

5 page(s) of revised draft labeling has been redacted from this portion of the review.

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/s/

Jeanine Best
8/15/03 10:31:35 AM
CSO

Toni Piazza Hepp
8/15/03 10:34:44 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-368
Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cialis (tadalafil).

We also refer to your May 27, 2003 Complete Response to our April 29, 2002 approvable letter.

We have completed our initial review and have determined that your application is sufficiently complete to permit a substantive review. Additionally, we also identified the following potential review issues:

Clinical

1. Data from the ritonavir and ketoconazole interaction study is under review. At this point in the review, we foresee the need to limit the dose to 10 mg and reduce the frequency of dosing in the group of patients taking concomitant "potent" CYP 450 3A4 inhibitors.

2. Data from the renal insufficiency studies are under review. At this point in the review, and taking all available data into account, we foresee recommending limitation of the dose to 10 mg in those patients with mild renal insufficiency. In those patients with moderate or severe renal insufficiency, we would prefer a 5 mg dose. Because such a dosage strength is currently unavailable, we foresee a potential labeling issue for this population, possibly in the form of a Contraindication or a Precaution.
[ ]

3. Considering the overall risk/benefit profiles for the 10 mg and 20 mg dosage strengths, as well as the pharmacokinetic data in young and in elderly subjects, we may ultimately recommend a 10 mg starting dose in the elderly. Titration up to 20 mg would still be acceptable.

4. You will need to clarify your guidance to patients in regard to alcohol use. Specifically, the Division believes that [redacted] does not provide sufficient guidance in this regard.

5. The interaction study with doxazosin is yet to be intensively reviewed. We believe that this will be a critical study for guiding safe use of Cialis, especially in regard to labeling. Additional

comments pertaining to this study will be conveyed to you as soon as possible following our review of the data.

6. All submitted data relevant to back pain and myalgia is under review. At this point in our review, our remaining concern regarding back pain is in those patients with moderate or severe renal insufficiency. In these patients, the incidence and severity of back pain appears to be greater than in other populations. This may require specific labeling and/or a lower dose in this particular population.

7. The nitrate interaction study is yet to be intensively reviewed. We believe that this also will be a critical study for guiding safe use of Cialis, especially in regard to labeling. Additional comments pertaining to this study will be conveyed to you as soon as possible following our review of the data.

Chemistry, Manufacturing and Controls (CMC)

There are no initial review issues at this time.

Clinical Pharmacology and Biopharmaceutics

The review of Study H6D-EW-LVFB is ongoing. To facilitate review, please submit the data from the Ibutilide dose-finding study electronically in SAS Transport File format. In addition, please provide your rationale for selecting ibutilide as the positive control for the QT study.

Pharmacology and Toxicology

There are no initial review issues at this time.

Statistics

There are no review issues at this time.

We are providing the above comments to give you preliminary notice of potential review issues. Our initial review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
8/13/03 05:52:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-368

Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
1209 Orange Street
Wilmington, DE 19801

Dear Dr. Melfi:

We received your July 15, 2003 correspondence on July 16, 2003, requesting a meeting to discuss the status of the review of the Complete Response. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.

Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].

Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm.

Your request for a meeting has been granted and it is scheduled for:

Date: September 11, 2003
Time: 10:30 AM - 12:00 PM
Location: TBD
The following representatives from CDER are invited: Drs. Daniel Shames, Mark Hirsch, Ashok Batra, Harry Handelsman, Rajiv Agarwal, Moo Jhong Rhee, Suzanne Thornton, Yangmee Shin, Venkat Jarugula, Leslie Kenna, Mike Welch, Ameeta Parekh and Ms. Margaret Kober, Eufrecina DeGuia and John Kim.

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
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/

Margaret Kober
7/25/03 02:03:18 PM
Chief, Project Management Staff

Meeting Minutes

Date: July 10, 2003 **Time:** 11:30AM – 12:30 PM **Location:** Parklawn Bldg. Conference Room "Potomac"

NDA 21-368 **Drug Name:** Cialis (tadalafil) tablets

Indication: treatment of erectile dysfunction

Sponsor: Lilly ICOS LLC

Type of Meeting: Guidance (Navigational)

Meeting Chair: Dr. Mark Hirsch **External Participant Lead:** Dr. Cathy Melfi

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Daniel Shames, M.D. – Director, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Eufrecina DeGuia – Regulatory Health Project Manager, DRUDP (HFD-580)
Venkat Jarugula, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Margaret Kober, R.Ph. – Chief, Project Management Staff, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Harry Handelsman, M.D. – Medical Officer, DRUDP
Leslie Kenna, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Suzanne Thornton, Ph.D. – Acting Pharmacology Team Leader, DRUDP (HFD-580)
Yangmee Shin, Ph.D. – Pharmacology Reviewer, DRDUP (HFD-580)
Mike Welch, Ph.D. – Statistics Team Leader, Office of Biometrics, (DB II) HFD-715

External Participants:
Cathy Melfi, Ph.D. – Senior Regulatory Research Scientist, Lilly
Susan Sullivan – Manager, Regulatory Affairs, ICOS
Jeff Hesselberg, MBA – Supervisor, Regulatory Affairs, ICOS
Jeff Emmick, M.D. – Clinical, Lilly
Ken Ferguson, Ph.D. – Chief Scientific Officer, ICOS
Mark Barbato, M.B.A. – Team Leader, Lilly
Greg Sides, M.D. – Medical Director, Lilly
Elizabeth Bearby, Pharm.D. – Regulatory Affairs, Lilly
David Goodkin, M.D. – Development and Chief Medical Officer, ICOS
Wei Shen, Statistician, Lilly
Carol Van Auwelaer, Regulatory Affairs, CMC, Lilly

Malcolm Mitchell, M.D. – Clinical Pharmacology, Lilly

Objective: To provide navigational guidance to the reviewers regarding content and format of the Complete Response electronic submission specifically the location of items addressing the the deficiencies in the Approvable letter.

Background: NDA 21-368, Cialis (tadalafil) was issued an Approvable (AE) letter on April 29, 2002, on the 10-month goal date. In response to the deficiencies, the sponsor re-submitted the NDA on May 27, 2003. The new goal date is November 28, 2003.

Discussion and Decision Points:

- The sponsor started off the meeting with an overview of the submission pointing out the location of the information addressing the deficiencies in the Approvable letter.
- The "super annotated label" in the submission includes hyper-links that link to information in current submission (blue links) or information in original NDA (red links).
- Lilly stated that they are seeking approval for 10 mg and 20 mg tablets, with 20 mg as starting dose.
- The Division indicated that 5 mg dose could be requested for use in some sub-populations but there is no definite decision yet. The sponsor will be notified of such decision.
- It was also indicated that a —mg dose could be considered as the starting dose for renally impaired patients and the elderly. The sponsor will be notified about this as well.
- The Division reiterated its position that the "worst case scenario" must be studied; specifically, to delineate the maximal inhibition with a potent 3A4 inhibitor (e.g. ritonavir). Discussion was held regarding the adequacy of the current ritonavir data.
- The Division reiterated its position that the doxazosin pharmacodynamic interaction study results would be critical in proposing safe drug use. These will be reviewed in detail.

Action Items:

- Lilly ICOS agreed to provide the following:
  - Most recent and updated Periodic Safety Report (PSUR)
  - Additional data to support the conclusions regarding interactions between Cialis and 600 mg bid ritonavir
- A 74-day "filing" letter will be issued by the Division on approximately August 10, 2003. This letter will state issues identified early on in the review; the sponsor hopes to clarify whether a 5 mg dose (and in what population) will be requested by the Division.
- A 4-month review meeting will be held in September; Lilly will be sending an official request.
- Response from the Chemistry team will be provided regarding the current facilities inspection status.
- Meeting minutes will be sent to the sponsor within 30 days.

(See appended electronic signature page)

Mark Hirsch, M.D.
Concurrence, Chair

NOTE: 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 outcome.

cc:
NDA Arch:
HFD-580/DeGuia/Shames/ /Hirsch/Batra/Handelsman/Kober
drafted: DeGuia071703
concurrences: Hirsch080403
final: DeGuia080503

MEETING MINUTES

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/s/

Mark S. Hirsch
8/7/03 10:19:03 AM
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-368

Lilly ICOS LLC
Attention: Cathie Melfi, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

We acknowledge receipt on May 28, 2003 of your May 27, 2003 resubmission to your new drug application for Cialis (tadalafil) tablet, 20 mg.

We consider this a complete, class 2 response to our April 29, 2002 action letter. Therefore, the user fee goal date is November 28, 2003.

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

Sincerely,

{See appended electronic signature page}

Eufrecina DeGuia
Regulatory Health 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/

Eufrecina deGuia
6/26/03 01:12:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-368

Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
1209 Orange Street
Wilmington, DE 19801

Dear Dr. Melfi:

We received your May 30, 2003 correspondence on June 2, 2003 requesting a meeting to provide an overview and navigation of your May 27, 2003 submission. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.

Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for
Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].

Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm.

You requested a type B meeting. The meeting is scheduled for:

Date: July 10, 2003
Time: 11:30am - 12:30pm
Location: Parklawn Conference Room C
Invited CDER participants:

Daniel Shames, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Donna Griebel, M.D. - Deputy Director, DRUDP
Mark Hirsch, M.D. - Medical Team Leader, DRUDP
Ashok Batra, M.D. - Medical Officer, DRUDP

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Leslie Kenna, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Alexander Jordan, Ph.D. - Pharmacology Team Leader, DRUDP
Yangmee Shin, Ph.D., Pharmacologist, DRUDP
Mike Welch, Ph.D., Biostatistics Team Leader
Margaret Kober, R.Ph. - Chief, Project Management Staff, DRUDP
Eufrecina "Freshnie" Deguia – Regulatory Project Manager, DRUDP (HFD-580)

Background information is not required for this meeting.

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
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/

Margaret Kober
6/13/03 12:26:36 PM
Chief, Project Management Staff

Meeting Minutes

Date: March 4, 2003 **Time:** 10:30AM – 12:00 PM **Location:** Parklawn Bldg. Conference Room "17-05"

NDA 21-368 **Drug Name:** Cialis (tadalafil tablets)

Indication: treatment of erectile dysfunction

Sponsor: Lilly ICOS LLC

Type of Meeting: Guidance (pre-Complete Response)

Meeting Chair: Dr. Daniel Shames **External Participant Lead:** Dr. Greg Sides

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Daniel Shames, M.D. – Director, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)
Donna Griebel, M.D. – Deputy Director, DRUDP (HFD-580)
Eufrecina DeGuia – Regulatory Health Project Manager, DRUDP (HFD-580)
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
George Benson, M.D. – Urology Team Leader, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkat Jarugula, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemistry Reviewer, Division of New Drug Chemistry (DNDC II) @ DRUDP (HFD-580)
Mike Welch, Ph.D. – Statistics Team Leader, Division of Biometrics @ DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Margaret Kober, R.Ph. – Chief Project Management Staff, DRUDP (HFD-580)
Yangmee Shin, Ph.D. – Pharmacology Reviewer, DRUDP (HFD-580)

External Participants:
Cathy Melfi, Ph.D. – Senior Regulatory Research Scientist, Lilly
Susan Sullivan – Manager, Regulatory Affairs, ICOS
Jeff Hesselberg, MBA – Supervisor, Regulatory Affairs, ICOS
Ken Ferguson, Ph.D. – Chief Scientific Officer, ICOS
Mark Barbato, R.Ph., M.B.A. – Team Leader, Lilly
Greg Sides, M.D. – Medical Director, Lilly
Elizabeth Sloan, Pharm.D. – Regulatory Affairs, Lilly
David Goodkin, M.D. – Development and Chief Medical Officer, ICOS

Jeff Emmick, M.D., Ph.D. – Clinical, Lilly
Steve Whitaker, M.D. – Clinical, ICOS
Sanjeev Ahuja, M.D. – Clinical, Lilly
Malcolm Mitchell, M.D. – Clinical Pharmacology, Lilly
Wei Shen, Ph.D. – Statistics, Lilly
David Miner, Ph.D. – Global Quality Leader, Manufacturing, Lilly
Carol Jan Auweler, R.Ph. – Regulatory Affairs, CMC, Lilly

Objective: To preview the contents of the upcoming Complete Response to the Approvable (AE) letter.

Background: NDA 21-368, Cialis (tadalafil) was issued an Approvable (AE) letter on April 29, 2002, on the 10-month goal date. During the "Communications" Meeting on February 10, 2003, the Division recommended that the sponsor should come in for a pre-Complete Response meeting to provide an overview of the data that will be included in the submission, and to receive the Division's comments. Meeting package dated February 17, 2003 was submitted.

Discussion and Decision Points:
After the initial presentation of the first three deficiencies by the sponsor, the following comments were provided by the Division addressing each deficiency:

#1: Nitrates

- Sponsor conducted an appropriate study.

- Interaction between nitrates and tadalafil 20mg is clear at 24 hours post- tadalafil dosing. Clinical review team differs with sponsor's interpretation in that we believe that there is still some evidence of an interaction out as far as 96 hours. For this, the most evidence comes from the endpoint: "decrease in systolic BP of >30 mm Hg upon standing".

- [redacted]

#2: Alcohol

- Sponsor conducted an appropriate study.

- Interaction between 0.7 gm/kg of ethanol and tadalafil 20mg is clear. However, the clinical review differs with the sponsor's interpretation of the magnitude and clinical significance of the interaction. For example, approximately 20% of patients in the combination group had a

standing systolic BP of <85 mm Hg and approximately 20% had a standing diastolic BP < 45 mm Hg. The Division believes this is a significant clinical risk.

- The current proposed labeling for this issue minimizes the risk information and does not accurately reflect the data from Table 2.2.

- The clinical review team points out that tadalafil alone (without alcohol) resulted in orthostatic hypotension in approximately 5% of patients in this study. FDA believes that tadalafil itself is a systemic vasodilator as demonstrated in this and in other trials.

#3: QT

- The sponsor has conducted a retrospective analysis of QT data from the original NDA submission and some new clinical QT data not submitted in the original NDA. They will also submit new HERG channel data. This material is not sufficient to resolve the deficiency because:
    a. The number of relevant patients from Studies LVBS, LVBG and LVBU are few. Relevant patients would require "high" blood concentrations, placebo controls, and serial EKGS at appropriate times post-dosing.
    b. Without an active control in any of these three studies, it will not be possible to state the exact magnitude of any (if any) mean QTc effect of tadalafil that the data serve to exclude.

- FDA believes that the results of Protocol LVFB must be submitted in order to ultimately resolve this deficiency.

- The sponsor submitted the final draft protocol for LVFB on October 11th after receiving comments from Dr. Stockbridge on October 7th. On October 7th, they stated that the study would initiate "shortly". The Division inquired: Has the study started? Are their any results yet? The sponsor stated that the study was ongoing.

#4: Myalgias/back pain

- The sponsor conducted appropriate retrospective and prospective analyses of this issue.

- The clinical review team points out that patients will need to be informed of the details of this adverse reaction in order to make their own risk/benefit analysis (e.g. need for pain medication, time of onset after dosing, duration of pain, severity of pain, etc).

- The Division inquired how many patients have undergone the prospective workup. The sponsor stated that approximately 130 patients had already undergone the work up.

- The pharmacologist inquired as to whether the sponsor had conducted skin biopsies to assess for immune complexes in vessels or whether sponsor had done serum immunoelectropheresis. The sponsor stated that no rashes or purpura were noted so no skin biopsies were done. In addition, the sponsor had not done immunoelectrophoresis.

#5 CMC

- The sponsor expressed their belief that the inspection of the Puerto Rico site is satisfactory. However, the site will still need to be inspected when the NDA is re-submitted.

FDA comments regarding each "additional" deficiency

Cardiovascular safety

- The sponsor conducted an extensive review of cardiovascular events in the NDA, did seek additional information on nine FDA "notable" patients (without any success in this search) and will also submit the results of the PET scan study and the treadmill study. This is all appropriate.

- The clinical review team requests an analysis of all cardiovascular events for the placebo-controlled studies only, similar to the analyses in Tables 3.3. and 3.4. These analyses should be based on frequencies of reported events, not corrected by patient-year.

- In the treadmill study (LVCP), when nitroglycerin was given after tadalafil or placebo in conjunction with exercise, there was a significant effect of tadalafil on inducing hypotension (30% of patients had sitting systolic BP <85 in the tadalafil group versus 4% in the placebo group). The Division considered this a signal of potential clinical risk. The sponsor should consider whether this finding has implications for risk management (such as chest pain after completion of intercourse). The sponsor should propose means of risk management.

Drug interactions

- The sponsor has conducted 4 new interaction studies and one new study in patients on multiple anti-hypertensive medications. These are all appropriate.

- Only 3 patients finished the ritonavir 600mg BID component of the ritonavir study (which is the recommended dosage strength). The remainder of the patients took only 200mg BID. The sponsor has not justified why 200mg BID is sufficient. It is possible that the data sponsor collected will be sufficient. This is a review issue.

- "Liver function abnormalities" were reported in 2 of 3 patients given tadalafil and ritonavir 600mg BID. The sponsor believes that this was ritonavir-related but the clinical review team requires further support for that judgement.

- In patients with untreated hypertension, or treated *but uncontrolled* hypertension, tadalafil significantly decreases blood pressure (but only modestly in those with controlled BP). The sponsor and clinical review team differ on the interpretation of magnitude of the risk. —

Visual effects

- The sponsor conducted an additional protocol which they claim Dr. Chambers approved during direct discussions. We do not have a record of Dr. Chambers' concurrence.

- Claims of "no tadalafil-related negative effects" (especially on color vision) must be fully endorsed by Dr. Chambers only after his review of the data from new Study LVFF.

- —

Safety in diabetics

- The sponsor informs DRUDP that no diabetic was excluded for orthostatic hypotension and additional new safety data in diabetics from 4 studies (including two U.S. Phase 3 trials) is available. This is appropriate.

A5. Applicability of non-U.S. data to U.S. patients

- There are two new U.S. Phase 3 trials with a total N of 402 (305 patients on tadalafil 20mg). This is appropriate.

Safety update

- The safety update is acceptable.

Starting dose: 10mg versus 20mg

- Sponsor — proposes 20mg starting dose but now allows for dose reduction to 10mg.

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[redacted]

- [redacted]

- [redacted]

[redacted] **Responsiveness**

- The exact wording for dosing instructions will be a review issue.

- On its face, the change from [redacted] to "at 30 minutes" is an improvement.

Additional Comments:

Statistical

- The sponsor's analyses attempt to show superior efficacy results for the 20 mg dose compared to the 10 mg dose to support their argument that the higher dose offers a therapeutic advantage. These analyses pool data from studies LVCO and LVDJ and apply methods and modifications to statistical endpoints that are retrospectively defined. The individual studies were not designed to show a statistical difference between doses, and the original statistical review found no evidence of statistical superiority for the 20 mg dose when studies were combined. The relevance of these new analyses to support 20 mg as a starting dose will be a review issue.

- The original statistical review addressed analysis deficiencies in trials LVDG [redacted] and LVCK [redacted], neither of which supported clear labeling decisions. In this submission, the sponsor summarizes results from these and other studies and indicates that a complete response, including the results from a new study, will be submitted. Determining the nature of any labeling language to describe duration of response and/or time to onset will be a review issue.

Pharmacology and Toxicology

- Regarding myalgia and back pain, Pharm/tox reviewer asked whether the sponsor has considered a possibility of immune-mediated hypersensitivity by the drug or its metabolite, and whether they tested the potential biomarkers: ANCA, Ig, *etc.*, since immune-mediated

hypersensitivity is the most common drug-induced vasculitis, and the symptoms of myalgia could be the initial presenting systemic manifestations.

- The sponsor did not test these specific biomarkers since they did not observe clinically significant changes in blood counts or in other general inflammatory parameters, and in skin rashes or other evidence of hypersensivity reaction.

Action Items:

- Meeting minutes will be sent to the sponsor within 30 days.

(See appended electronic signature page)

Daniel Shames, M.D.
Concurrence, Chair

NOTE: 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 outcome.

cc:
NDA Arch:
HFD-580/DeGuia/Shames/Griebel/Hirsch/Batra/Parekh/Kober/
Benson,Jarugula,Welch
drafted: DeGuia030503
concurrences: Shin, Batra,Jordan,Benson,Welch031703Hirsch,Jarugula, Parekh, Shames031803
final: DeGuia031903

MEETING MINUTES

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/s/

Daniel A. Shames
3/24/03 04:33:32 PM

Meeting Minutes

Date: February 10, 2003 **Time:** 10:30AM – 12:00 PM **Location:** Parklawn Bldg. Conference Room "B"

NDA 21-368 **Drug Name:** Cialis (tadalafil tablets)

Indication: treatment of erectile dysfunction

Sponsor: Lilly ICOS LLC

Type of Meeting: Guidance (Communications)

Meeting Chair: Dr. Daniel Shames **External Participant Lead:** Dr. Tim Franson

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Florence Houn, M.D., M.P.H. – Director, Office of Drug Evaluation III
Daniel Shames, M.D. – Director, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)
Eufrecina DeGuia – Regulatory Health Project Manager, DRUDP (HFD-580)
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Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Margaret Kober, R.Ph. – Chief Project Management Staff, DRUDP (HFD-580)
Max Koppel, M.D. – Medical Reviewer, DRUDP (HFD-580)

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Ken Ferguson, Ph.D. – Chief Scientific Officer, ICOS
Mark Barbato, M.B.A. – Team Leader, Lilly
Greg Sides, M.D. – Medical Director, Lilly
Jen Stotka, M.D. – US Regulatory Affairs, Lilly
Elizabeth Sloan, Pharm.D. – Regulatory Affairs, Lilly
David Goodkin, M.D. – Development and Chief Medical Officer, ICOS

Objective: To discuss expected interaction and communications between Lilly ICOS and the Division during the review of the NDA.