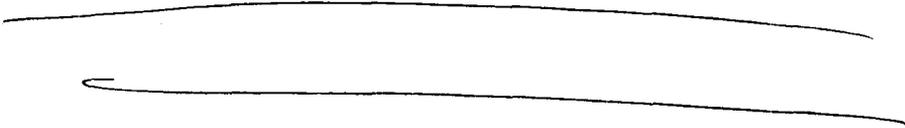


the 6-month safety data is derived from Study LVBL, wherein all 1169 patients received the 10 mg dose for one month prior to up-titration to 20 mg.

3. **The total number of medically significant cardiovascular adverse events in the entire NDA was so small as to preclude adequate assessment of potential relationship to Cialis.** These events include syncope, angina pectoris, chest pain, arrhythmia, myocardial infarction, heart failure, cerebrovascular accident, and cardiac arrest. There were a few reports of these types of events occurring during the immediate post-dosing period. These could be plausibly related to Cialis. In order to absolutely rule out Cialis as the cause of these events, very large controlled trials might be necessary. Are such trials possible or necessary in the pre-marketing period? In the post-marketing period? Would studies of surrogate markers be useful? For example, the sponsor has actively ongoing trials assessing the potential effect of Cialis on coronary blood flow using PET scanning and on cardiac stress test performance in men with stable angina. My final recommendation on this issue at this moment would be to:
 - a. obtain the results from coronary artery PET scanning (LVBZ).
 - b. obtain the results from stress testing in patients with stable coronary artery disease (LVCP).
 - c. obtain the results from a larger and better controlled QT study.
 - d. request the sponsor derive QTc data from Study LVBS (using dosage strengths up to 500 mg).
 - e. request the sponsor submit a detailed analysis of the effect of Cialis on the cardiovascular system (from all NDA data sources), and
 - f. review this entire "cardiovascular package" in consultation with the Division of Cardio-Renal Drug Products and/or the Cardio-Renal Advisory Committee.
4. **Assessments of the interaction with nitrates were not adequate to fully appreciate and manage the risk to those patients who have urgent need for therapy with nitrates after taking Cialis.** This is particularly relevant to Cialis due to its approximately 17 hour half-life which is prolonged by 5 hours in the elderly and by perhaps even longer in men with renal insufficiency.
5. **Assessments of the QT interval were not adequate to completely assess the potential for Cialis 20 mg to prolong the QT interval.** Assessments of QT were not conducted at high enough doses, nor with enough patients. Assessments of the potential for the metabolite methylcatechol glucuronide to prolong QT were not conducted.
6. **Assessment of safety of the 20 mg dose in patients with clinically significant renal insufficiency were not adequate to assess risk in that population.** Based upon the diminished clearance in patients with at least mild renal insufficiency, the resultant increase in exposure by two times, the resultant prolongation of exposure to tadalafil metabolites, and the limited safety information at those exposures (e.g. following doses of 40 mg and higher), it is not possible to predict safety outcomes in this population. This concern is compounded by the exclusion of patients with clinically significant renal insufficiency in the clinical trials and the increased incidence of unexplained adverse events (e.g. myalgias and back pain) in these patients in clinical pharmacology trials.
7. **Assessments of safety in the diabetic population were not adequate to assess risk in that population.** Only 119 diabetics received 20 mg in all Phase 3 pivotal trials combined and of that total, only 47 were not pre-screened for the presence of orthostatic hypotension at baseline (as in Study LVBK).

8. **Assessments in humans to explain the pathophysiology of the adverse event terms “myalgia” and “back pain” were not adequate.** I believe that there is a need to provide reasonable assurance in humans that these symptoms do not reflect medically significant underlying pathophysiology. The sponsor has not aggressively sought the etiology of these symptoms. This concern is compounded by the fact that the incidence and severity of myalgias and back pain appear to increase with higher dose and higher exposure to tadalafil.
9. **The potential for interaction between tadalafil and alcohol as evidenced by findings in the 10 mg dosage strength study has not been acknowledged by the sponsor.** There are no labeled precautions nor warnings for this potential interaction.
10. **Interactions between some anti-hypertensive medications and tadalafil have not been conducted at the 20 mg dose. In addition, some interactions with the 10 mg dosage strength have not been fully acknowledged by the sponsor.** The potential for more significant and severe drug interactions in the renally and hepatically impaired has not been considered.
11. **Assessments of interactions with warfarin and with aspirin were not conducted with the 20 mg dosage strength.** This is particularly relevant given the recognized potential for phosphodiesterase inhibition to adversely effect platelet function.
12. **Assessments of an interaction between Cialis and certain widely used alpha-adrenergic antagonists were not conducted.** In this respect, potential for interaction was conducted using the alpha blocker least likely to show an interaction (tamsulosin). This is especially important since many of the same middle-aged and elderly men who will receive Cialis are also candidates for concomitant treatment for symptoms of benign prostatic hypertrophy (BPH).

Other deficiencies that are significant in my view but do not rise to the level of a “not approvable” deficiency are listed below:

1. The Division of Scientific Investigation’s (DSI) decision not to conduct routine inspections of all relevant pivotal trials is considered an outstanding item in the FDA’s review. Given the relative paucity of medically significant adverse events in the entire Phase 3 program and disparities in adverse event reporting incidences between Canada, Australian, and U.S. trials and the others (e.g. Taiwan and Spain), I advocate inspection of each trial that is intended to support the approval of Cialis.
2. The sponsor should describe the percentage of patients in the Phase 3 trials who previously used sildenafil, who previously responded to sildenafil, and who previously tolerated sildenafil. In addition, the sponsor does not make plainly evident that there were no sildenafil “failures” included in the Phase 3 clinical program.
3. 
4. There is a single manufacturing site in Indiana (Eli Lilly) for which the final recommendation from Office of Compliance is pending. At this moment, there appears to be good manufacturing practice (GMP) deficiencies.

5. Assessments of effects on vision were so flawed as to provide little useful data (as per Dr. Chambers). The sponsor should conduct new studies in order to assess the impact of tadalafil on vision.

2. Background

Erectile dysfunction (ED) has been defined as the inability of the male partner to attain and maintain an erect penis in the context of the overall sexual experience. Over the past decade, our understanding of the condition has rapidly advanced. It is well-recognized that many, if not most cases of erectile dysfunction have an "organic" component. In fact, we have come to realize that vascular smooth muscle dysfunction is a major reason for ED. We now understand ED to be a multifaceted disease impacted by numerous systemic forces including atherosclerosis, diabetes, renal insufficiency, heart disease, smoking, alcohol use, other endocrinopathies, traumatic injury, neurologic dysfunction, psychological disturbances, concomitant medications, among a plethora of other conditions and factors.

For years, practitioners have been faced with these patients, often in urgent need of help for this condition. For quite some time, the only available modalities of treatment were psychological counseling, unapproved and approved herbal therapies, devices such as the vacuum erection device (VED), and surgical implantation of semi-rigid and (recently) inflatable rods. Over the last few years, there has been a rapid advancement in the understanding of pharmacologic modalities to help patients.

Intracavernosal pharmacotherapy; that is, the use of vasodilating medications injected directly into the corpora cavernosa is now an available modality (e.g. injectable alprostadil or Caverject). Various mixtures of unapproved and approved vasodilators have been administered directly into the penile shafts of such patients. These drugs include papaverine, phentolamine, vasoactive intestinal polypeptide, and alprostadil. Unfortunately, drawbacks of such therapy include fear of injection, injection pain, drug-related penile pain, and prolonged erection/priapism. Eventually, most patients withdraw from injection therapy.

Intraurethral vasodilating medications are also approved for ED (e.g. alprostadil or MUSE). These suppositories "melt" upon insertion into the urethra and "seep" through the penile tunics into the corpus spongiosum and cavernosa and are supposed to act similarly to the direct injection of such substances. The advantage of an intraurethral suppository is clear: insertion of a pellet into the meatus is associated with less fear and discomfort than a direct injection. This modality is also limited by its route, by direct penile pain, by occasional systemic blood-pressure lowering effect, and by modest efficacy.

Of greatest prominence has been the addition of Viagra (sildenafil citrate) to the ED armamentarium. Sildenafil is a selective inhibitor of Type 5 cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE). By inhibiting the action of this phosphodiesterase, sildenafil enhances the vasodilating effect of endogenous nitric oxide (NO) in the penile corpora. This allows for the enhanced influx of arterial blood to the corpora following the neurologic signal for release of NO and ultimately, prolongation and intensification of the hardness of the erection. It is administered orally as "on-demand" therapy approximately 1 hour prior to sex. Its use has been limited by several factors including: the lack of spontaneity, commonly reported adverse reactions such as dyspepsia, rhinitis, headache, flushing and blue vision. Of greatest concern has been its potentially (and actual) life-threatening interaction with nitrates, a modest

interaction with other anti-hypertensives, and of course, the fairly large number of reports of myocardial infarction and sudden death among users during the last 3 years. While there is clearly a linkage between adverse outcomes and the nitrate/sildenafil interaction, it has been impossible to "dissect out" an actual sildenafil-related effect in the infrequent cardiovascular events. This is due to confounding factors in middle-aged and elderly men including chronic diseases, concomitant medications, concomitant sexual activity after long periods of abstinence, and a huge number of users. Limited clinical pharmacology experiments (both in human trials, in-vivo and in-vitro experiments), data from controlled trials, and data from international observational cohorts has not revealed a direct role for sildenafil in these events. And, in fact, the number of such cases did drop after a November 1998 labeling change which may have encouraged more judicious usage in men with advanced heart disease. The event number has declined continuously since then.

Cialis (or tadalafil or IC351) is a novel Type 5 PDE inhibitor. It was pursued by the ICOS Corporation initially because of its potential to improve upon Viagra. It has a prolonged half-life (17 hours) and therefore would allow for a longer period of potential responsiveness. It was originally thought to be more selective for the "penile" of Type 5 PDE. However, early results still demonstrated a significant systemic interaction with nitrates, implying a less than selective effect on the systemic vasculature. In addition, it was also notable that such adverse events as dyspepsia, rhinitis and vasodilation were not uncommon, again implying a lack of clinically improved selectivity for PDE5 over sildenafil. Evidence of effect on the "retinal" PDE (or Type 6) was thought to be less of a problem than with Viagra, and that still may ultimately prove to be a benefit (although it is not yet supported as one). Of concern, however, even from the earliest IND stages, the occurrence of **vague complaints of "back pain" and diffuse "myalgias"** were reported when IC351 was given in high doses to volunteers. Also of concern were the findings of "arteritis" in beagle dogs. While these findings were qualitatively similar to those in dogs given sildenafil, the exposures at these doses were similar to or below those being given to man in the early tadalafil trials. In fact, studies for tadalafil were on IND "Clinical Hold" until the sponsor agreed to lower the doses by upwards of 10-fold and follow patients for clinical evidence of arteritis.

At the time of the presumed End-of-Phase 2 (EOP2) meeting, it became clear that a similar toxic effect on animal testes was happening. Therefore, the sponsor was told at the EOP2 meeting that the FDA recommended that they refrain from initiating Phase 3 U.S. trials until the testes-damaging effect was disproved in humans. The sponsor planned and conducted two U.S. "semen safety" trials. Nevertheless, while these trials were in progress, the sponsor planned, designed and conducted an entire Phase 3 controlled and open-label, efficacy and safety development program overseas (e.g. South America, Mexico, Canada, Taiwan, Australia and Europe). This was carried out with no specific agreement from FDA. However, the Division had previously provided the sponsor with some guidance on the "general elements" of Phase 3 trials in ED (e.g. endpoints, designs, durations, eligibility criteria, among other issues). After finishing this international program, the sponsor requested and we held a pre-NDA meeting.

Therefore, the critical times in this IND were:

1. Submission of the IND (November 6, 1997) and subsequent Clinical Hold (December 9, 1997).
2. Lifting of the Clinical Hold (July 29, 1998).
3. Meeting with the sponsor for purposes of providing "general comments" and "general guidance" (June 9, 1999).
4. Meeting with the sponsor at the "would-be" EOP2 meeting (August 30, 1999)
5. The Pre-NDA meeting (February 21, 2001)

3. Design of the program and clinical trials to support the indication

3.1. Overall program

In support of the clinical efficacy and safety of Cialis for the treatment of erectile dysfunction (ED), the sponsor submitted the results from the following sixteen (16) clinical efficacy and safety trials in males with ED:

1. Six (6) Phase 3 trials (herein referred to as the "Phase 3" or "pivotal" trials)
2. Three (3) active-controlled trials (the "active-comparator" trials)
3. Three (3) placebo-controlled trials designed to assess time-to-onset of action and duration of responsiveness (the "supplementary" trials)
4. Four (4) Phase 2 dose-ranging trials (the "Phase 2" trials).

In support of the safety of chronic administration of Cialis, the sponsor also submitted results from the following eight (8) clinical safety trials:

1. Four (4) open-label safety studies (LVBL, LVBD, LVDR, and DSD07 [LVBE]).
2. Two (2) placebo-controlled studies investigating the effect of Cialis on semen characteristics (LVCD and LVCZ).
3. Two (2) controlled studies investigating of the effect of Cialis on vision (LVAN and LVCN).

There were approximately forty additional studies conducted as part of the Clinical Pharmacology and Human Pharmacokinetics evaluation. These are discussed separately in Dr. Roy's review and the relevant section of this memo.

3.2. The "pivotal" (N=6)

The burden for supporting efficacy and safety for Cialis falls predominantly on the six Phase 3 (or "pivotal" trials). These were:

LVBN – conducted at 19 investigative sites in Canada, Mexico and Argentina from December 1999 to May 2000 (placebo, 5 mg and 10 mg, N=215).

LVBK – conducted at 18 investigative sites in Spain from December 1999 to August 2000 (placebo, 10 mg, and 20 mg, N=216).

LVCE – conducted at 18 investigative sites in Canada from March 2000 to August 2000 (placebo, 2.5 mg, 5.0 mg, and 10 mg, N=311).

LVCO – conducted at 4 investigative sites in Australia from September 2000 to February 2001 (placebo and 20 mg, N=140).

LVCO – conducted at 8 investigative sites in Taiwan from October 2000 to February 2001 (placebo, 10 mg, 20 mg, N=196).

LVDJ – conducted at 25 investigative sites in Canada from October 2000 to April 2001 (placebo, 10 mg and 20 mg, N=253).

All of these six trials were designed similarly. These were randomized, double-blinded, placebo-controlled, parallel-arm design trials with the objective of evaluating the safety and efficacy of intermittent (or "on-demand") dosing of different doses of Cialis compared to placebo in men with ED. All trials consisted of two phases; first, a four-week no-treatment baseline period followed by a 12-week, double-blind treatment period. Patients were evaluated at the following timepoints: a screening visit (prior to the baseline period), a baseline visit (after the baseline period) and monthly visits during the treatment period.

The primary timepoints of interest were at Visit 2 (baseline) and Visit 5 (Week 12 or endpoint). The primary efficacy endpoint was the same in all three trials. In that regard, the primary endpoint was actually tripartite and included the following items:

1. the 30-point Erectile Function (EF) domain of the International Index of Erectile Function (IIEF).
2. Question #2 of the Sexual Encounter Profile (SEP), a per-event diary, that asks specifically "Were you able to insert your penis into the partner's vagina?", and
3. Question #3 of the SEP, that asks specifically "Did your erection last long enough for you to have successful intercourse?".

Each of these three endpoints was calculated as a mean change-from-baseline. For the two SEP endpoints, the assessments reflect mean per-patient change-from-baseline event rates. The Division's goal in advising this three-part primary endpoint is to allow straightforward clinical interpretation of small changes in EF domain score. The IIEF is a fully validated patient-reported outcome instrument; however, the Division has occasionally struggled with the "clinical relevance" of small changes from baseline or small differences between drug and placebo. Secondary endpoints were numerous and included among others, all other domains from the IIEF, individual questions from the IIEF, results of the total patient SEP, results from the partner SEP, results from the Global Assessment Question, etc. The statistical analysis plan called for the comparison of change-from-baseline for each endpoint between each drug group and placebo at an alpha level of 0.05 for each endpoint.

The patient eligibility criteria were virtually identical between trials. The inclusion criteria called simply for men aged 18 and older with "erectile dysfunction" of at least 3 months duration, a monogamous, stable, heterosexual relationship, and at least 4 attempts made during the baseline period. ED was defined as "a consistent change in the quality of erections that adversely affected the patient's satisfaction with sexual intercourse". Exclusion criteria were numerous and included the following relevant items:

1. Impotence caused by other primary sexual disorders including premature ejaculation or impotence caused by untreated endocrine disease.
2. History of radical prostatectomy or other pelvic surgery with subsequent failure to achieve erection.
3. History of penile implant or evidence of clinically significant penile deformity.
4. Evidence of **clinically significant renal insufficiency** within 6 months prior to Visit 1.
5. Evidence of clinically significant hepatobiliary disease as evidenced by AST/SGOT or ALT/SGPT >3 times ULN at Visit 1.
6. Hemoglobin A1c >13% at Visit 1.
7. Patients with chronic stable angina treated with long-acting nitrates, or patients with chronic stable angina who required short acting nitrates within the last 90 days.
8. Angina occurring during sexual intercourse in the last 6 months.

9. Patients with unstable angina, specifically, those meeting the criteria for Class I, II, or III of the Braunwald Classification of Unstable Angina.
10. History of myocardial infarction or coronary artery bypass graft surgery within 90 days prior to Visit 1, or percutaneous coronary intervention within 90 days of Visit 1.
11. Any supraventricular arrhythmia with an uncontrolled ventricular response (mean heart rate >100 bpm) at rest despite medical or device therapy.
12. History of spontaneous or induced sustained ventricular tachycardia response (mean heart rate >100 bpm for at least 30 seconds) despite medical or device therapy.
13. Presence of an internal cardioverter-defibrillator.
14. History of cardiac arrest despite medical or device therapy.
15. **Any evidence of congestive heart failure, specifically, NYHA Class 2 or above.**
16. Significant conduction defect within 90 days prior to Visit 1.
17. Systolic blood pressure >170 or <90 mm Hg, or diastolic BP >100 or <50 mm Hg at screening; or patients with malignant hypertension.
18. History of significant central nervous system injury within the last 6 months, including stroke or trauma.
19. History of HIV infection.
20. Current treatment with nitrates, cancer chemotherapy, or anti-androgens.
21. History of drug, alcohol, or substance abuse within the last 6 months.
22. **Prior ineffective treatment with sildenafil citrate.**
23. Any condition that would interfere with the patient's ability to provide informed consent or comply with study instructions, would place patients at increased risk, or might confound the interpretation of the study results.

There were minor design differences between the six pivotals. These include the following:

1. Only four of the six pivotal trials studied the 20 mg dosage strength (LVBK, LVCQ, LVCO and LVDJ).
2. LVBK (Spain) enrolled only diabetics, although well-controlled diabetics were not excluded from other trials.
3. In LVBK (Spain, diabetic-only), patients who met criteria for "orthostatic hypotension" at screening were excluded.
4. LVCQ (Australia) was submitted in interim study report format at Week 12 of the treatment period, but was actually continued as a placebo-controlled study for a total of 24 weeks and was submitted in its entirety as an amendment to the NDA.
5. LVCQ (Australia) was the only study to compare only 20 mg to placebo and not to any other dosage strength.
6. All studies randomized patients evenly between treatment groups except for the two trials conducted last: LVDJ (placebo: 10 mg: 20 mg = 1:2:2) and LVCQ (placebo: 20 mg = 1:2)

Reviewer's comments:

1. In general, these pivotals were adequately designed to assess efficacy. However, I have concerns regarding the overall assessment of safety:
 - a. The number of patients per treatment group per study was small and this serves to limit optimal assessment of drug safety in any individual trial.
 - b. The total number of diabetic patients who received the 20 mg dose was 119. Of those, 72 were pre-screened for the absence of baseline orthostatic hypotension.
 - c. Data from Taiwan and Spain revealed lower incidences of the most frequent adverse events for both the 10 mg and 20 mg dose compared to the other trials. The reason for this difference is unclear.

2. **It is concerning that all patients with “clinically significant” renal insufficiency were excluded in light of the increased exposure to drug and metabolite in patients with mild and moderate renal insufficiency and the increased incidence of the unexplained adverse events “back pain” and “myalgia” in that population.**
3. While there were no “sildenafil failures” in these trials (and that is acceptable), it was not made clear how many patients were actually former “sildenafil responders”. A high percentage of sildenafil responders would enrich these trials for both efficacy and for safety.

3.3. The “active-comparator trials” (N=3)

The three active comparator trials were identified and designed as follows:

LVBO - was a placebo and active-controlled, double-blinded, double-dummy, parallel arm-design trial comparing Cialis to placebo and to Viagra as “on-demand” therapy for men with ED

Four hundred twelve (412) patients were randomized to three arms (placebo, Cialis and Viagra). A 12-week active treatment period was preceded by a 4-week baseline period. **The study compared a dose-titration regimen of 5 mg and 10 mg of Cialis to 50 mg and 100 mg of Viagra and to a similarly titrated placebo.** The primary endpoints were the EF domain of the IIEF, SEP Question #2, and SEP Question #3. Secondary endpoints included other IIEF and SEP data

The study was conducted at 34 investigative centers in the Belgium, France, Germany and The Netherlands from November 1999 to May 2000.

Reviewer’s comment:

1. **A dose-titration regimen of Cialis using 5 mg to 10 mg was clearly superior to placebo.**
2. **Cialis (5 mg to 10 mg) was not shown to be statistically non-inferior to Viagra (50 mg to 100 mg) in this trial. After this study, all pivotal trials were designed to study Cialis 20 mg.**

LVCF – was a double-blinded, double-dummy, two-period, two-sequence, active-control, crossover design-trial comparing Cialis 10 mg to Viagra 50 mg as “on-demand” therapy for ED. Fifty-seven (57) men with ED were randomized. The duration of each treatment period was 4 weeks separated by a 2-week washout and preceded by a 2-week no-treatment baseline. The primary endpoint was “patient preference” but quantitative indices of erectile function were also assessed (e.g. IIEF and SEP data).

The study was conducted in 5 investigative centers in the United States from May 2000 to September 2000.

Reviewer’s comment: Cialis 10 mg was statistically non-inferior to Viagra 50 mg in both the EF domain score of the IIEF and the primary endpoint, patient preference.

LVCY – was a double-blinded, double-dummy, active-control, two-period, four-sequence, crossover-design trial comparing Cialis 20 mg to Viagra 50 mg and comparing Cialis 20 mg to Viagra 100 mg. Ninety-one (91) men with ED were randomized. The duration of each treatment period was 4 weeks separated by a 2-week washout and preceded by a 4-week no-treatment baseline. The primary endpoint was the EF domain of the IIEF. Secondary endpoints included SEP data and other quantitative indices of erectile function.

The study was conducted in 6 investigative centers in the United States from January 2001 to April 2001.

Reviewer's comment: Cialis 20 mg was statistically non-inferior to Viagra 100 mg in the EF domain score of the IIEF.

3.4. The three “supplementary” trials (N-3)

Three (3) placebo-controlled trials were conducted with the objective of assessing _____ of action and _____ of responsiveness. These were:

LVBJ – was a randomized, double-blind, double-dummy, placebo-controlled, two-period, crossover study comparing a single dose of 10 mg _____ formulation to a single dose of the 10 mg _____ formulation in terms of *percentage of patients with _____ of a “Rigiscan-confirmed” adequate erection within 30 minutes of dosing*. This study was conducted in 61 male patients at 4 U.S. investigative sites.

LVCK – was a randomized, double-blind, double-dummy, placebo-controlled parallel arm study comparing 10 mg, 20 mg and placebo in terms of the _____ *of an adequate erection within the first 30 minutes after dosing*. In this trial, patients were tested for _____ after each of 4 attempts. The study was conducted in 223 male patients at 10 U.S. investigative sites.

LVDG – was a randomized, double-blind, placebo-controlled parallel arm study comparing 20 mg and placebo in terms of *the efficacy of single doses at 24 hours and at 36 hours* after dosing. The total number of attempts made by a given patient was four (two at each timepoint). The study was conducted in 348 male patients at 34 investigative sites in the U.S., France, Spain, Germany, Sweden and Denmark.

Reviewer's comments:

1. The Rigiscan _____ study (LVBJ) is considered exploratory due to its dependence on Rigiscan and its censoring of data at 30 minutes.
2. The clinical _____ study (LVCK) is also considered exploratory due to its censoring of data at 30 minutes.
3. The _____ of responsiveness study (LVBG) was not appropriately designed to actually test _____, but rather efficacy at a given time point. It does appear that Cialis is statistically more effective than placebo in some patients at 24 hours and 36 hours after dosing.

3.5. The "Phase 2" trials (N=4)

The four Phase 2 trials were originally identified as DSD01, DSD04, DSD06, and DSD08. These were renamed LVBI, LVBG, LVBF, and LVAC, respectively. These studies were conducted using a precursor formulation _____ of the to-be-marketed _____ formulation. They also studied doses as high as 100 mg. Given the increased C_{max} with the _____ formulation when compared with the _____ formulation and the higher doses used in Phase 2, these studies provide relevant data for potential safety risks and for exploration of the relationship between pharmacokinetics and pharmacodynamics.

DSD01 (LVBI) was a randomized, double-blind, placebo-controlled, two period, two-sequence, crossover study comparing placebo to 100 mg. The endpoint of interest was cumulative duration of erection as measured by RigiScan-study after a single dose. Forty (40) men with ED were randomized at three sites in The Netherlands. This first IC351 clinical study was conducted from November 1997 to March 1998.

DSD04 (LVBG) was a randomized, placebo-controlled, parallel-arm design study comparing placebo to doses of 10 mg, 25 mg, 50 mg and 100 mg. Patients received daily dosing for 21 days. The primary endpoints of interest were Questions #3 and #4 of the IIEF. Two hundred ninety-four patients (294) were randomized at 19 investigative sites in Belgium, France, Germany, and the Netherlands. The study was conducted from May 1998 to October 1998.

DSD06 (LVBF) was a randomized, placebo-controlled parallel-arm design study comparing placebo to doses of 2 mg, 5 mg, 10 mg and 25 mg. Patients received 14 "on-demand" doses over a treatment period of 21 days. The primary endpoints of interest were Questions #3 and #4 of the IIEF. One hundred seventy-nine patients (179) were randomized at 13 investigative sites in the United States. This was the first human study conducted under IND# 54,553. The study was conducted from September 4, 1998 to December 7, 1998.

Reviewer's comment: It is notable that even doses as low as 2 mg _____ were found to be effective in this U.S. trial. The sponsor believes that a therapeutic effect "plateau" was reached at doses "between 10 mg and 25 mg" _____

DSD08 (LVAC) was a randomized, placebo-controlled parallel-arm design study comparing placebo to doses of 2 mg, 5 mg, 10 mg and 25 mg. Patients received "on-demand" doses (no more than once daily) over a treatment period of 21 days. The primary endpoints of interest were Questions #3 and #4 of the IIEF. Two hundred twelve patients (212) were randomized at 10 investigative sites in the Canada. The study was conducted from April 1999 to August 1999.

Reviewer's comment: It is again notable that 2 mg was found effective in terms of attaining an erection (Question #3) but not in maintaining an erection (Question #4). The sponsor concluded that 5 mg was the lowest effective dose in this Canadian study.

Reviewer's comment: The results from these Phase 2 studies must be analyzed in light of the higher doses of _____ formulation compared to the to-be-marketed formulation.

3.6. The “open-label safety” studies (N=4)

The sponsor conducted 4 open-label, dose-titration type, safety studies. Two of these provide a limited amount of information. They are:

DSD07 (LVBE) - was a 10-week, open-label, dose-titration safety extension of Phase 2 trials.

LVDR - was an open-label, safety extension of pivotal studies LVDJ (Canada) and LVCQ (Australia). It includes 331 patients enrolled at 23 investigative sites. It was initiated on February 2001 and therefore had generated very little data at the time of the March 2001 data cut-off for the original NDA. Limited safety data from this trial was submitted in the final March 18, 2002 safety update.

Therefore, essentially two safety studies (LVBD and LVBL) carry the burden of supporting chronic safety in this NDA, as follows:

LVBD was an open-label, dose-titration study in men who had previously participated in a Cialis trial. Doses and duration of study were 5 mg, 10 mg, 25 mg and 50 mg, _____, and 5 mg, 10 mg and 20 mg (market-image) for up to 2 years. The study was terminated prematurely “as the Sponsor determined the scientific objectives of the study had been met.” All patients, except those that “rolled-over” from DSD07 (LVBE), started on the 5 mg dose and were titrated up incrementally only if the investigator found that after an adequate number of attempts that the patient could not achieve satisfactory intercourse. Patients who had rolled-over from DSD07 initiated this trial at their “preferred dose” from DSD07. Dose level could be decreased incrementally if a patient experienced an adverse event that persisted or interfered with daily activity and the investigator believed that the event was related to drug. Once an optimal dose had been achieved, the patient was to remain on that dose unless further dose modification was “needed”. Two hundred and three (203) men were enrolled at 19 investigative sites in Belgium, France, Germany and the Netherlands. The study was conducted from November 1998 to May 1999.

Reviewer’s comments:

1. Most patients initiated LVBD at doses of 10 mg and higher.
2. The sponsor states that 143 patients received at least 20 mg for at least 12 months. **This comprises roughly two thirds of the 1-year safety experience submitted in the original NDA.** It is unclear if this experience represents continuous use of 20 mg or continuous use with the option for intercurrent down-titration (either in this study or in DSD07) or with the initiation of lower doses followed by up-titration. Since all these patients participated in some previous Cialis study in Belgium, France, Germany and the Netherlands, at least some started therapy on 10 mg in Study DSD04.
3. It appears that some investigators exercised the option to down-titrate some patients to 10 mg and 5 mg based on adverse events.
4. Given the dose-titration design in this study (LVBD) and in the preceding Study DSD07 (LVBE), this reviewer believes that the safety of chronic treatment with 20 mg without the option for titration cannot be accurately assessed from the results of this trial.

5. It is noted that a transition from _____ to market image occurred during this study.

LVBL was an open-label, dose-titration study in men who had previously participated in a Cialis trial. Doses and duration of study were 5 mg, 10 mg, and 20 mg. The study was ongoing at the time of original NDA submission. The total maximal duration of participation in the trial was 18 months in order to generate 2-years of safety data in some patients. **All patients in this trial started on the 10 mg dose and were titrated up or down incrementally, "following specific titration rules, up to a maximum on-demand dose of 20 mg per day."**

One thousand one hundred seventy-three (1173) men were enrolled at 69 investigative sites in Argentina, Belgium, Canada, France, Germany, Italy, Mexico, Spain, and the Netherlands. The study was initiated on August 1999 and is still ongoing. Safety cut-off date for the original NDA was March 1, 2001.

Reviewer's comments:

1. Study LVBL accounts for the majority of chronic 6-month exposure to 20 mg and about one third of the one-year exposure. The fact that ALL patients began treatment in LVBL with at least one's month supply of 10 mg poses a real problem in interpreting the bulk of the safety data that supports fixed-dose Cialis 20 mg (with no option for titration).

3.7. The "semen characteristics" studies

Based upon findings in dogs of testicular atrophy and seminiferous tubular degeneration at doses that may have been comparable to projected human exposures, the sponsor undertook two controlled human trials to answer the question of potential risk to human spermatogenesis. These studies were identified as LVCD and LVCZ. LVCD (10 mg) was submitted as part of the original NDA. An interim report of LVCZ (20 mg) was submitted to the original NDA and the final study report was submitted as an NDA amendment.

LVCD – was a randomized, placebo-controlled, parallel group design study comparing 10 mg daily and placebo. The objective of the trial was to assess the effect of 10 mg daily for 26 weeks on sperm concentration. The study was designed as a "non-inferiority" design to placebo where the primary endpoint was the percentage of patients in a group with at least 50% reduction in sperm concentration at any assessment. Two hundred and four (204) subjects were randomized at 9 U.S. sites.

LVCZ – had the identical design except for the administration of 20 mg daily for 26 weeks.

Reviewer's comment: As opposed to effects noted in dogs, there did not appear to be any effect of Cialis at either dose on human sperm.

3.8. The "vision studies"

Based upon the drug class and the potential for effects on retinal function, the sponsor carried out two special safety studies designed to investigate the effect of Cialis on vision. The reader is referred to Dr. Chambers' consultation report (and the appropriate section of this memo) concerning the design and procedures for Studies LVAN and LVCN.

4. Clinical results to support the indication

4.1 Clinical efficacy

The six “pivotal”, four “Phase 2”, three “comparative” studies and three “supplementary trials” provide a large body of controlled efficacy data. **My overall conclusion is that Cialis 20 mg is effective in the treatment of erectile dysfunction.**

However, major questions remain:

1. *Is there a dose(s) of Cialis that is lower than 20 mg and that is also effective?*

In brief, this reviewer believes that doses of 10 mg and 20 mg were **both** clearly shown to be effective in at least 2 adequate and controlled fixed-dose studies in patients with ED.

The 5 mg dosage strength was also shown to be statistically better than placebo in five of the six required endpoints in two trials. For the 5 mg dose, the mean changes-from-baselines in EF domain scores were 4.1 and 5.0. While the clinical relevance of the 5 mg data could be argued, I think it is probably sufficient to support approval.

Therefore, I believe that all three doses are effective individually. Moreover, I believe that all three could probably be used even more effectively when titrated in the management of ED.

If all three doses are effective, should only the lowest dose be approved? Since I do not believe that a single dose of 5 mg would serve the needs of all ED patients, the real question is whether 20 mg provides any therapeutic benefit over 10 mg. Strictly in terms of efficacy, I do not believe that the sponsor has shown that the 20 mg dose is more efficacious than 10 mg in the broad population. Therefore, the only reasonable argument appears to be that the 20 mg dose is more effective than the 10 mg dose in a subgroup (e.g. more severe ED). While this is likely to be true, I believe it requires additional support.

The following efficacy tables are derived from six pivotal trials as follows and are provided here for the reader’s benefit:

Table 1. Summary of primary efficacy analyses for Study LVBN (Canada-Argentina-Mexico):

	Placebo (n=69) End (change)	Cialis 5 mg (n=72) End (change)	Cialis 10 mg (n=74) End (change)
ED domain of IIEF	15.0 (+0.7)	17.9 (+4.0) p=0.006	20.0 (+5.6) p < 0.001
SEP 2	48.5 (+5.6)	57.3 (+14.5) p=.063	73.2 (+29.0) p < 0.001
SEP 3	26.2 (+3.7)	37.6 (+19.0) p=0.040	58.2 (+31.7) p < 0.001

Table 2. Summary of primary efficacy analyses for Study LVBK (Spain-diabetics only):

	Placebo (n=71) End (change)	Cialis 10 mg (n=73) End (change)	Cialis 20 mg (n=72) End (change)
ED domain of IIEF	12.2 (+0.1)	19.3 (+6.4)*	18.7 (+7.3)*
SEP 2	29.9 (-4.1)	56.7 (+22.2)*	54.4 (+22.6)*
SEP 3	20.0 (+1.9)	48.0 (+28.4)*	41.8 (+29.1)*

*p<0.001

Table 3. Summary of primary efficacy analyses for Study LVCE (Canada):

	Placebo (n=76) End (change)	Cialis 2.5 mg (n= 74) End (change)	Cialis 5.0 mg (n=79) End (change)	Cialis 10 mg (n=79) End (change)
ED domain of IIEF	14.4 (+1.1)	16.6 (+3.2) p=.154	17.5 (+5.1) p= .002	20.6 (+6.0) p<.001
SEP 2	45.9 (+2.4)	55.9 (+15.3) p=0.31	55.9 (+17.6) p=0.008	68.4 (+15.1) p=.001
SEP 3	27.8 (+3.5)	37.2 (+19.7) p=.014	41.5 (+24.0) p<.001	51.1 (+25.8) p<.001

Table 4. Summary of primary efficacy analyses for Study LVCQ [at three months only] (Australia):

	Placebo (n=47) End (change)	Cialis 20 mg (n=93) End (change)
ED domain of IIEF	13.0 (-1.3)	23.7 (+7.7) p<0.001
SEP 2	42.4 (-7.2)	81.3 (+26.5) p<0.001
SEP 3	26.2 (+0.4)	74.1 (+40.7) p=0.<0.001

Table 5. Summary of primary efficacy analyses for Study LVCO (Taiwan):

	Placebo (n =66) End (change)	Cialis 10 mg (n=65) End (change)	Cialis 20 mg (n=66) End (change)
ED domain of IIEF	18.1(+2.6)	22.6 (+8.1)*	25.0 (+8.0)*
SEP 2	54.5(+9.5)	76.9 (+34.5)*	84.9 (+35.3)*
SEP 3	42.8 (+14.7)	70.0 (+47.9)*	78.0 (+49.7)*

* = p<0.001

Table 6. Summary of primary efficacy analyses for Study LVDJ (Canada):

	Placebo (n=50) End (change)	Cialis 10 mg (n=103) End (change)	Cialis 20 mg (n=100) End (change)
ED domain of IIEF	14.5(-0.9)	21.2 (+6.6)*	23.3 (+8.0)*
SEP 2	45.3(-6.4)	72.5 (+21.3)*	76.0 (+21.3)*
SEP 3	31.9 (+4.9)	56.7 (+32.8)*	61.5 (+29.0)*

* = p<0.001

2. *Is there a dose-regimen that is effective in the treatment of ED patients using Cialis?*

The sponsor studied dose-titration regimens of 5 mg, 10 mg and 20 mg in the context of the long-term safety studies. These did not specifically focus on efficacy.

Only one trial investigated the effect of dose-titration on efficacy in a blinded and well-controlled fashion (Study LVBO). As described above, this was a placebo and active-controlled, double-blinded, double-dummy, parallel arm-design trial comparing Cialis to placebo and to Viagra as “on-demand” therapy for men with ED. The study compared a dose-titration regimen of 5 mg and 10 mg of Cialis to 50 mg and 100 mg of Viagra and to a similarly titrated placebo. The primary endpoints were the EF domain of the IIEF, SEP Question #2, and SEP Question #3. Secondary endpoints included other IIEF and SEP data (see Table 6). The active treatment period was 12 weeks.

Table 7. Summary of efficacy results from LVBO

	Placebo (n=129) End (change)	Cialis 5-10 mg (n=136) End (change)	Viagra 50-100 mg (n=139) End (change)
ED domain of IIEF	13.3 (+0.5)	19.8 (+ 6.4)	23.0 (+ 9.3)
SEP 2	38.9 (-0.7)	62.8 (+22.1)	76.6 (+29.6)
SEP 3	20.9 (+4.4)	47.1 (+31.8)	64.1 (+42.3)

These results reveal that Cialis at a dose-titration regimen of 5 to 10 mg is statistically and clinically effective in the treatment of men with ED. However, at these dose ranges, Cialis was not statistically non-inferior to Viagra. The sponsor argues that in the subgroup of men with “moderate ED” Cialis 5 to 10 mg was not inferior to Viagra 50 to 100 mg. However, in men with mild and severe ED, Cialis was inferior.

Reviewer’s comment: I believe that this results (from this one study) clearly demonstrate that the 5 mg to 10 mg Cialis regimen is effective in the treatment of ED. While interesting, I do not feel compelled to approve a higher dose regimen of Cialis simply to match Viagra results.

3. *What should we tell users and prescribers about the _____ of Cialis?*

It is my feeling that the _____ studies were flawed. First, Rigiscan results are difficult to apply to the actual clinical scenario. Second, both studies censored data at 30 minutes from dosing. Therefore, regarding _____ (in essence, when to take the tablet), I recommend that the future label give patients the same instructions as clinical trial subjects were given in the pivotal trials. These instructions were simply to take Cialis “prior to anticipated sexual activity”. As for the _____ the sponsor presents one study showing that the Cialis-treated patients fared better at Hours 24 and at Hour 36 after drug administration. This data can be put directly in the future label without drawing any particular conclusion.

Reviewer's comments: In the Phase 3 "active comparator" trials, only 91 patients received the dose requested for approval and only for 4 weeks "on-demand". This is also not a feasible amount of data for good review.

In the three "supplementary trials", a total of 385 patients received Cialis:

- 61 patients received a single dose of 10 mg
- 74 patients received four single doses of 10 mg
- 250 patients received four single doses of 20 mg

Reviewer's comments: In these "supplementary trials, 250 patients received the 20 mg dose but only for a maximum of 4 attempts. Again, this is an inadequate amount of data.

In the four "Phase 2 trials", a total of 595 patients received Cialis:

- 40 patients received a single dose of 100 mg
- 77 patients received 2 mg "on-demand" for 21 days
- 81 patients received 5 mg "on-demand" for 21 days
- 78 patients received 10 mg "on-demand" for 21 days
- 79 patients received 25 mg "on-demand" for 21 days
- 60 patients received 10 mg daily for 21 days
- 58 patients received 25 mg daily for 21 days
- 59 patients received 50 mg daily for 21 days
- 59 patients received 100 mg daily for 21 days

Reviewer's comments:

1. Some meaningful safety data may be derived from the 195 patients in the Phase 2 studies who received 25 mg or higher doses either daily (N=177) or "on-demand" (N=79) for 21 days.
2. Twenty-one (21) days is still considered a limited duration of time for good assessment of adverse events.

In the two major "open-label" safety studies (LVBD and LVBL), a total of 1376 patients received Cialis:

- 1173 patients enrolled in Study LVBL. All these persons received a starting dose of 10 mg (for one month) and all were allowed to titrate between 5, 10 and 20 as needed for up to two years.
- 203 patients enrolled in Study LVBD. Doses included 5 mg, 10 mg, 25 mg and 50 mg — and 10 and 20 mg market-image (upon switch in formulations). Doses were titrated as needed.

In the two other "open-label" safety studies (LVBE and LCDR), a total of 525 patients received Cialis:

- 194 patients enrolled in Study LVBE.
- 331 patients enrolled in Study LVDR

4.2.3. Overall adverse events

Adverse event terms were qualitatively similar across trials but differences in incidences were apparent between trials. It is the intent of this reviewer to focus on the 20 mg dose with occasional reference to the 10 mg and to higher doses for a frame of reference.

The most commonly reported adverse events were **dyspepsia, headache, back pain, rhinitis, “flu syndrome”, “infection”, myalgia and vasodilatation.**

In the four Phase 3 pivotal trials that included the 20 mg dose, the following commonly reported adverse events and their incidences were reported:

Table 8. Incidences of commonly reported AEs in LVCO (Taiwan)

	Placebo (n=66)	IC351 10 mg (n=65)	IC351 20 mg (n=65)
Dyspepsia	1 (1.5%)	6 (9.2%)	6 (9.2%)
Headache	3 (4.5%)	3 (4.6%)	4 (6.2%)
Back pain	2 (3.0%)	7 (10.8%)	5 (7.7%)
Rhinitis	6 (9.1%)	4 (6.2%)	4 (6.2%)
Myalgia	0	6 (9.2%)	6 (9.2%)
Infection	4 (6.1%)	3 (4.6%)	6 (9.2%)
Dizziness	4 (6.1%)	3 (4.6%)	4 (6.2%)
Cough increased	5 (7.6%)	3 (4.6%)	3 (4.6%)

Reviewer’s comment: Reported incidence of myalgias was high in this Taiwan study. One could speculate an increased IC351 and IC351 metabolite exposure in Taiwanese men with resultant increase in myalgia incidence.

Table 9. Incidences of commonly reported AEs in LVBK (Spain/diabetics only)

	Placebo (n=71)	IC351 10 mg (n=73)	IC351 20 mg (n=72)
Dyspepsia	0	8 (11.0%)	8 (11.1%)
Headache	2 (2.8%)	7 (9.6%)	6 (8.3%)
Back pain	1 (1.4%)	1 (1.4%)	4 (5.6%)
Flu syndrome	3 (4.2%)	3 (4.1%)	3 (4.2%)
Myalgia	1 (1.4%)	4 (5.5%)	3 (4.2%)

Table 10. Incidences of commonly reported AEs in LVDJ (Canada)

	Placebo (n=50)	IC351 10 mg (n=103)	IC351 20 mg (n=100)
Dyspepsia	1 (2.0%)	10 (9.7%)	22 (22.0%)
Headache	4 (8.0%)	15 (14.6%)	17 (17.0%)
Back pain	1 (2.0%)	5 (4.9%)	7 (7.0%)
Flu syndrome	5 (10.0%)	8 (4.9%)	5 (5.0%)
Myalgia	2 (4.0%)	5 (4.9%)	4 (4.0%)
Infection	11 (22.0%)	20 (19.4%)	11 (11.0%)
Pain	1 (2.0%)	10 (9.7%)	8 (8.0%)
Rhinitis	2 (4.0%)	6 (5.8%)	4 (4.0%)
Vasodilatation	2 (4.0%)	4 (3.9%)	6 (6.0%)

Reviewer's comments:

1. The adverse event term "pain" in this study (LVDJ) is unclear. What types of "pain" were reported?
2. The adverse event term "vasodilatation" in this study (LVDJ) is unclear. What symptoms and signs were reported under the heading "vasodilatation"?

Table 11. Incidences of commonly reported AEs in LVCQ (Australia)

	Placebo (n=47)		IC351 20 mg (n=93)	
	@3mos	@6mos	@3 mos	@6mos
Dyspepsia	0	0	17 (18.3%)	20 (21.5%)
Headache	3 (6.4%)	4 (8.5%)	22 (36.6%)	40 (43.0%)
Back pain	6 (12.8%)	7 (14.9%)	11 (10.8%)	15 (16.1%)
Pharyngitis	0	2 (4.3%)	5 (8.6%)	
Myalgia	1 (2.1%)	1 (2.1%)	8 (8.6%)	9 (9.7%)
Vasodilatation	0	0	4 (5.4%)	6 (6.5%)
Diarrhea	2 (4.3%)	4 (8.5%)	7 (7.5%)	9 (9.7%)
Arthralgia	2 (4.3%)	5 (10.6%)	4 (6.5%)	7 (7.5%)
Cough increased	2 (4.3%)	2 (4.3%)	6 (5.4%)	5 (5.4%)
Pharyngitis	0	2 (4.3%)	5 (8.6%)	

Reviewer's comments: The Canadian and Australian results reveal higher incidences of most commonly reported adverse events compared to the Taiwanese and Spanish trials. This is difficult to explain.

Both semen concentration studies provide relevant AE data based upon their daily dosing, placebo controls, and 6 month duration.

Table 12. Incidences of commonly reported AEs in LVCD (U.S.)

	Placebo (n=101)	IC351 10 mg (n=103)
Dyspepsia	1 (1.0%)	18 (17.5%)
Headache	5 (5.0%)	18 (17.5%)
Back pain	4 (4.0%)	12 (11.7%)
Myalgia	0	6 (5.8%)
Asthenia	0	4 (5.8%)
Arthralgia	0	3 (2.9%)
Infection	5 (5.0%)	3 (2.9%)

Table 13. Incidences of commonly reported AEs in LVCZ (U.S.)

	Placebo (n=106)	IC351 20 mg (n=111)
Dyspepsia	4 (1.0%)	18 (19.8%)
Headache	4 (5.0%)	18 (19.8%)
Back pain	2 (1.9%)	6 (10.8%)
Infection	8 (4.0%)	12 (14.4%)
Myalgia	2 (1.9%)	4 (8.1%)
Rhinitis	7 (6.6%)	3 (4.5%)
Cough increased	6 (5.0%)	3 (3.6%)

Reviewer's comments:

1. The unexplained adverse event terms myalgia, back pain, and arthralgia are concerning to this reviewer. I do not believe that the sponsor has made a sufficient effort to explain these event terms. These appear to increase in incidence with duration of exposure and with renal insufficiency. I remain concerned that these may represent unexplored medically significant pathophysiology.
2. The event terms myalgia and back pain appear to increase in incidence in the Phase 2 trials in the 25 mg groups.
3. Myalgia and back pain were reported as severe and prolonged in patients receiving the 50 mg and 100 mg dose.
4. The results in U.S. may be somewhat inflated by daily dosing and use in a generally healthy population.

4.2.4 Deaths

There were no deaths in any of the four Phase 2 trials or the six pivotal Phase 3 trials. There were no deaths in the three "supplementary" Phase 3 trials. There were no deaths in the clinical pharmacology trials. There were no deaths in the sperm studies. There was one (1) death in one of the three "active comparator" Phase 3 studies.

Patient #602-6077 in LVCY died while in the Cialis 20 mg period of this crossover trial. He was a 35-year old, 260 pound non-insulin dependent diabetic. He collapsed after 15 minutes on a treadmill in a gym, he received CPR and was pronounced dead on arrival at an emergency room. An autopsy revealed significant narrowing of all main coronary arteries. His widow could not find his diaries or medications but **she stated that his last dose was 45 minutes prior to going to the gym.** The investigator reported the death as unrelated to drug.

Reviewer's comment: There is a temporal relationship to drug as per the widow. The fact that no medications or diary could be located is a deficiency.

At the time of the 4-month safety update, there were six (6) total deaths reported in the open-label trials at the time of the original NDA. These were all in open-label trial LVBL. Of these, two were due to cancer (prostate cancer and cholangiocarcinoma) and one was suicide by hanging. Of the remaining three, one patient died in his sleep, one collapsed while dancing, and one died after a game of golf.

Patient 007-3072 was a 56-year old generally healthy male found dead in his hotel room. He was taking concomitant Hytrin. According to his widow he was “away on work” when he passed away. The widow was unable to locate any diaries or medications. Time of last dosage was unknown. The investigator reported the death as unrelated to study drug. An autopsy report revealed left ventricular hypertrophy and subaortic stenosis. It was the opinion of the coroner that death was due to arrhythmia

Reviewer’s comment:

Blood pressure lowering effect of tadalafil with Hytrin is theoretically detrimental in patients with subaortic stenosis. The fact that no medications or diary could be located is a deficiency.

Patient 105-2107 was a 71-year old diabetic, hypertensive male who collapsed while dancing. He was taken to the hospital and found to be having an anterior wall myocardial infarction. He was mechanically ventilated. He died of aspiration pneumonia. Of note, two months prior to his death he was evaluated for an elevated CPK enzyme. His medications and diaries were never found. Time of last dosage was unknown. The investigator deemed the event as unrelated to drug.

Reviewer’s comment: The fact that no medications or diary could be located is a deficiency.

Patient 043-4065 was a 68-year old male with a history of previous myocardial infarction. He was taking concomitant Hytrin. Just following a game of golf, he complained of a burning sensation in his neck, collapsed and turned blue. He was pronounced dead on arrival. Autopsy results revealed the presence of old infarct but none recent. Coronary atherosclerosis was extensive. Recent hemorrhage into a plaque was observed. The cause of death was considered to be an arrhythmia. No study medication or diaries were retrieved. Time of last dosage was unknown. The investigator deemed the event as unrelated to drug.

Reviewer’s comment: The fact that no medications or diary could be located is a deficiency.

Reviewer’s comment: The fact that study medication and diaries were not returned in any of these patients is concerning from a regulatory perspective.

4.2.5. Serious adverse events

In the original NDA, fifteen (15) patients reported serious adverse events (SAE) in the six **pivotal Phase 3 trials**. Nine (9) of these were in Cialis patients (0.9%) and 6 were in placebo (1.6%). The sponsor notes that two patients had myocardial infarctions in the placebo group but none in the drug group. There were no particularly notable SAEs in the pivotal trials. There were an additional 5 SAEs in the 3-month controlled extension of Study LVCQ; none of these were notable.

Reviewer's comment:

1. The size of the Phase 3 pivotal study database is so small as to preclude meaningful comparisons to placebo or solid conclusions about the drug-relatedness of such rare events as myocardial infarctions, strokes or death.
2. The differences in quality and quantity of serious adverse events in the pivotal trials compared with open-label Study LVBL is impressive.

There were three SAEs in the three **active-controlled trials** and none in the **supplementary Phase 3 trials**. There were 14 SAEs in the **Phase 2 trials**. None of these were notable.

Two notable SAEs were reported with Cialis in the **sperm studies (daily dosing)**, and these were:

Patient 314-5042 in the 20 mg study (LVCZ) was hospitalized for abdominal pain, fever, diarrhea, diminished hemoglobin and occult blood in the stool. The sponsor invoked the diagnosis of "gastroenteritis secondary to food poisoning". The investigator deemed the event not related to study drug.

Patient 305-1267 in the 10 mg study (LVCD) was admitted with periumbilical pain, watery diarrhea, and fever. Diagnostic tests were negative and the sponsor invoked the diagnosis "acute gastroenteritis". The investigator believed that this event was not related to drug. This same patient was re-admitted to hospital with severe left-sided thoracolumbar **back pain** that radiated to both lower extremities. While the patient had a history of lumbar laminectomies in the early 1970's, he had no chronic back pain until this event. The investigator believed that this event was "possibly" related to drug.

Reviewer's comments:

1. Gastroenteritis with heme-positive stools, abdominal pain, and fever were thus reported as an SAE in at least two trials. I am hesitant to simply dismiss this finding as not drug related. Diarrhea was reported in the controlled trials at a slightly higher incidence than placebo.
2. Severe back pain requiring hospitalization is a plausible adverse reaction to tadalafil.

In the **open-label safety studies** (including results from LVDR submitted on March 18, 20002):

•In **LVBD**, there were nine (9) serious adverse events reported in the original NDA. All nine of these were considered unimpressive.

•In **LVBL**, where most of the patients were enrolled, there were fifty-five (**55**) serious adverse events in the original NDA, twenty-eight (**28**) new serious adverse events in the 4-month safety update, and thirteen (**13**) new serious adverse events in final safety update.

Reviewer's comments:

This reviewer believes that many of these events (including syncope, gastrointestinal events, myocardial infarction, and angina pectoris) are relevant to assessment of the potential risk of Cialis.

Herein, some of these are depicted in narrative form. Cases that are not from LVBL are noted:

Syncope/Hypotension

Patient 005-0201 was a 53-year old man who stated that while driving on the highway, he became nauseous, had blurred vision, felt weak, and lost consciousness. He had been on study drug for approximately 8 months and his last dose was about 28 hours prior to the event. The patient recovered consciousness when the ambulance personnel arrived. Subsequent investigations revealed no injury and cardiologic and neurologic evaluation were unrevealing. The investigator assessed the event as “loss of consciousness” (**syncope**) and possibly related to study drug.

Reviewer’s comment: Syncope is a plausible adverse reaction to tadalafil. This narrative could signal the potential for vasodilatory AEs at times distant from dosing (e.g. 28 hours).

FROM STUDY LVCR (as derived from final safety update):

Patient 817-8600 was a 58-year old man who was hospitalized for chest pain in the early a.m., on the day after taking Cialis. In the emergency room, he was reported to receive sublingual and topical nitroglycerin. His blood pressure decreased after nitrate administration and was “difficult to reverse” (sic). Even though the nitropaste was wiped off at 4 a.m., he remained profoundly hypotensive at 6 a.m (BP 76/40). He was stable enough to be moved to a holding area in the E.R. at 8 a.m. Ultimately, he was diagnosed with esophageal spasm. The sponsor believed that administration of Cialis one day before could be related to the hypotension but so could insufficient removal of the nitropaste.

Gastrointestinal events

Patient 005-4118 was a 49-year old man who had a history of hypertension and coronary artery disease and had been taking aspirin for coronary artery disease prevention, developed gastroesophageal reflux. Five weeks later, he was hospitalized for abdominal pain and vomiting “coffee ground” secretions. Upper gastrointestinal endoscopy with biopsy revealed esophagitis and superficial chronic gastritis, and *Helicobacter pylori*. Following hospital discharge, the patient experienced nausea with subsequent dosing with study drug and discontinued from the study. This patient was taking study medication virtually daily for two weeks prior to the day of the event and on the day of the event. The investigator deemed that the event was possibly related to drug.

Reviewer’s comment: Coffee-ground vomitus and abdominal pain is not an implausible adverse event following tadalafil.

Myocardial infarction

Patient 007-0236 was a 65-year old man with a history of diabetes mellitus, hypertension, smoking and obesity. Four days after the last dose of study drug, the patient developed weakness, dyspnea, nausea, and chest pain. He was hospitalized and diagnosed to have had a **myocardial infarction**. The investigator assessed the event as possibly related to study drug.

Patient 405-1064 was a 73-year old diabetic hypertensive male who was reported as having several “hypoglycemic reactions” while participating in the study. He had also had some episodes of “chest pain”. During the management of one of the hypoglycemic episodes, a **myocardial infarction** was diagnosed on the basis of electrocardiography and abnormal cardiac enzymes. The case report form lists the event as having occurred one day after the last dose of medication.

A stress test done later was reported as showing "silent ischemia". The investigator assessed the event as unrelated to study drug.

Patient 002-0126 was 46-year old diabetic, hypertensive Asian male who hospitalized as a result of a **myocardial infarction** and unstable angina. The case report form lists the event has having occurred two days after the last dose of drug. The investigator considered the event unrelated to drug.

Patient 102-2036 was a 68-year old man with a history of diabetes mellitus and hypertension. Fourteen days after his last dose (by diary), the patient had an episodes of chest pain with radiation to both arms. He was hospitalized and diagnosed with **myocardial infarction**. Angiography showed multi-vessel stenoses and angioplasty with stent was performed. The investigator assessed the event as possibly related to study drug.

Reviewer's comment: The CRF does not contain documentation of returned tablets.

Patient 220-3256 was a 68-year old man with a history of diabetes mellitus. Ten days after his last dose (by diary), the patient had an episode of chest pain with radiation to both arms. He was hospitalized and diagnosed with **myocardial infarction**. Angiography showed multi-vessel stenoses and angioplasty with stent was performed. The investigator assessed the event as possibly related to study drug.

Reviewer's comment: The CRF does not contain documentation of returned tablets.

Angina pectoris

Patient 002-4017 was 50-year old diabetic hypertensive who was hospitalized as a result of **unstable angina**. The event occurred four days after the last dose of study medication. The patient underwent coronary angioplasty. The investigator considered the event unrelated to drug.

Patient 003-4062 was 46 year old hypertensive male on Hytrin who reported **chest pain** and dyspnea while playing tennis. He was admitted to the hospital and nitropaste was applied in the emergency room. All tests were negative for cardiac pathology. The case report form lists the event has having occurred one day after the last dose of drug. The investigator considered the event unrelated to drug.

Patient 405-1056 was 64 year old male smoker who was hospitalized for **angina pectoris**. The event occurred one day after the last dose of drug. Coronary angiography revealed moderate stenosis of three arteries. The investigator considered the event possibly related to drug.

Patient 817-8600 was 58 year old hypertensive male who was hospitalized for **chest pain**. The event occurred eight days after receiving his first dose. Upper endoscopy 1 month prior to the event revealed the presence of a perigastric tumor. The investigator considered the event possibly related to drug.

Reviewer's comment: The actual CRF as submitted with the 4-month SU did not contain an adverse event report for the hospitalization. This reviewer could not find a final diary or documentation of returned tablets. The sponsor stated that follow-up of this patient would be provided with the final study report for LVBL. As of this moment, LVBL is ongoing.

Cerebrovascular accident (CVA)

Patient 411-1129 was 64 year old male who awoke one day with aphasia, right-sided hemiparesis, and slurred speech. MRI showed an infarction in the left basal ganglia. The patient was left with residual functional impairment of the right hand and aphasia. This event, cerebral infarction, occurred three days after receiving his last dose. The investigator considered the event unrelated to drug.

Patient 408-1084 was reported to have a disturbance of speaking, later reported as an "apoplectic insult", and finally as a "cerebral infarct". On that day, the patient was also noted to have new-onset atrial fibrillation. This event, cerebral infarction, occurred approximately 1 month after receiving his last dose (per the diary). However, the investigator, _____ noted the actual stop date to be 3 days after the event. The investigator considered the event unrelated to drug.

Reviewer's comment: The last dose by diary and the official estimated stop date differ. This reviewer was unable to locate documentation of returned tablets.

Patient 004-4087 was 72 year old diabetic mellitus, hypertensive male was hospitalized who with a stroke of left arm and leg. The event occurred five months after receiving his last dose. The investigator considered the event unrelated to drug.

Reviewer's comment: The CRF does not contain documentation of returned tablets.

The final safety update for this NDA was submitted on March 18, 2001. It contained updated safety information for Studies LVCR (U.S.), LVDR (Australia and Canada), and LVBL.

For LVCR, there were 4 SAEs and three of these were "carotid occlusion", "chest pain", and "esophagitis" (see case above). There were eight discontinuations and one of those was for "angina pectoris".

For LVDR, there were fourteen SAEs and one was "myocardial infarction". There were 7 discontinuations for AEs, and none were cardiovascular in nature but others included "myalgias", "dyspepsia", and "eye disorders".

Finally, for LVBL, there was a total of 86 SAEs reported for the entire study (up to that point), with 12 new SAEs and one follow-up of a death. Of these, only the death was cardiovascular in etiology. There were 8 new discontinuations and only one was for "transient ischemic attack". Other included "dyspepsia", "headaches", "back pain", "vomiting" and "nausea".

Reviewer's comment: Given the time frame for review, these events could not be scrutinized in greater detail.

5. Major issues from other disciplines or other sources

5.1 Clinical pharmacology and biopharmaceutics (OCPB)

As a final recommendation for action on this NDA, OCPB recommended: “approval of an additional lower strength of 10 mg tadalafil.”

OCPB made this recommendation based on the following insights:

1. They believed that 10 mg dose strength would be “sufficient” for efficacy for most patients patients with erectile dysfunction (at least all of those with mild to moderate ED). They based this conclusion on a pharmacodynamic/pharmacokinetic model that largely used data from Phase 2 studies.
2. They believed that a dose of 20 mg in those patients with renal compromise resulted in higher incidence of myalgias and back pain in clinical pharmacology trials.

Drs Roy, Jarugula and Parekh’s review provided several important pieces of information:

Regarding ADME:

1. Tadalafil is rapidly absorbed after oral administration. T_{max} is approximately 2 hours. Rate and extent of absorption is not affected by food.
2. Tadalafil is widely distributed in bodily tissues with a volume of distribution of approximately 63 L.
3. Tadalafil is extensively metabolized. Mass-balance studies showed 61% excreted in the feces and 36% in the urine. Tadalafil is mainly metabolized by the CYP3A4 hepatic enzyme oxidation to its catechol metabolite. The catechol metabolite is extensively methylated and glucuronidated to form the methylcatechol and methylcatechol glucuronide conjugates. The methylcatechol glucuronide (MCG) is the major metabolite in human plasma and urine. The MCG is not selective for PDE5.
4. **The MCG is primarily cleared by the renal route.** The exposure to MCG in patients with moderate renal insufficiency is 3.5 times higher than in normals. This increase in exposure appears to be associated with a higher incidence of the adverse events myalgia and back pain in clinical pharmacology trials. In these patients, the onset of these particular adverse events was roughly 20 hours after peak plasma concentrations of tadalafil and coincided with high MCG levels.

Regarding pharmacokinetics

1. Area under the concentration time curve (AUC) increased dose-proportionately from 2.5 mg to 20 mg. On the other hand, maximum plasma concentration (C_{max}) increased less than proportionately at doses higher than 20 mg.
2. Steady-state plasma concentrations were attained at Day 5 of daily dosing and were approximately 1.6 times higher than the single dose values (accumulation was noted). Concentrations of the MCG were also almost 3 times higher at steady-state than after single doses.
3. Systemic exposure to tadalafil was decreased by 20% in diabetics compared with normals. Mean half-life in diabetics was actually 3 hours less.
4. Systemic exposure to tadalafil was increased by 25% in the elderly compared to the young. This finding was believed to be due to mildly decreased creatinine clearance (17%) in the elderly. **Tadalafil half-life was 5 hours longer in the elderly than in the young.**

Regarding renal and hepatic impairment

1. Mild and moderate hepatic impairment did NOT alter the metabolic clearance of tadalafil. Those exposures were similar to normals. Severe hepatic impairment patients were not studied.
2. On the other hand, systemic exposure was 2-fold higher in subjects with mild or moderate renal impairment. Renal impairment had a greater effect on disposition of the MCG than on the parent drug. In one clinical pharmacology study, the incidence of adverse events was highest in the group with moderate renal impairment (83%), less high in the mildly impaired group (20%) and lowest in the normal (12.5%). Dr. Roy's review states that "Due to the increased incidence of adverse events in the moderately impaired subjects, no subjects with severe renal impairment received tadalafil."

Reviewer's comments:

1. The relationship between degree of renal insufficiency, exposure to MCG, and the incidence of the adverse event terms "myalgia" and "back pain" is clinically very important.
2. The sponsor noted in a fax dated March 5, 2002 that Study LVDT is ongoing in patients on hemodialysis, however, to my knowledge, these results were not submitted for our review.

Regarding pharmacokinetic drug-drug interactions

1. Concomitant ketoconazole, a CYP 3A4 inhibitor, increased exposure to tadalafil by approximately 100%.
2. Concomitant rifampin, a CYP 3A4 inducer, reduced exposure by approximately 88%.
3. Daily dosing with tadalafil appeared to hasten the metabolism of midazolam, with small reductions in its AUC (13%) and Cmax (14%). This may implicate tadalafil as a mild inducer of CYP 3A4.

Regarding pharmacodynamic drug-drug interactions

1. Pharmacodynamic drug-drug interaction studies were conducted with tadalafil 10 mg for the following eight drugs. These are listed herein with their most relevant results:
 - a. *Nizatodine*
 - b. *Maalox* – (delayed rate of tadalafil absorption).
 - c. *Theophylline* – (increase in mean tadalafil levels, increase in mean heart rate in active-active combination group).
 - d. *Warfarin* – (no potentiation of anticoagulation).
 - e. *Metoprolol* – (additional reduction in systolic/diastolic blood pressures of 1-9/2-5 mm Hg compared to placebo; increased incidence of clinically significant BP changes).
 - f. *Bendrofluazide* – (additional reduction in systolic/diastolic blood pressures of 3-10/2-6 mmHg compared to placebo).
 - g. *Enalapril* - (additional reduction in systolic/diastolic blood pressures of 3/4 mm Hg, compared to placebo; increased incidence of clinically significant BP changes).
 - h. *Aspirin* – (no potentiation of prolonging bleeding).

Reviewer's comments:

1. There appears to be a minor pharmacodynamic interaction between tadalafil (10 mg) and each antihypertensive studied. Interactions with complicated, multi-drug antihypertensive regimens are impossible to predict but could be worse.

2. **None of these studies were re-done using tadalafil 20 mg.** It does not seem possible to extrapolate some of these results (e.g. theophylline, warfarin, metoprolol, bendrofluazide, and aspirin) to the 20 mg dose. This is considered an NDA deficiency.
2. Pharmacodynamic drug interaction studies were conducted with tadalafil **20 mg** for the following three drugs:
- Lovastatin* – (no significant increase in lovastatin levels).
 - Tamsulosin* – (additional reduction in supine systolic blood pressure of approximately 5-10 mm Hg, compared to placebo).
 - Angiotensin II receptor antagonists* – (additional reduction in mean ambulatory BP ranging from 3 to 21 mm Hg, compared to placebo; increased incidence of clinically significant decreases).

Reviewer's comment: The sponsor chose to study tamsulosin rather than less selective but widely used alpha antagonists.

3. Interaction with amlodipine was studied with both the **10 mg and 20 mg** dosage strengths.

Amlodipine + 10 mg – (additional reduction in systolic/diastolic blood pressure of 7/4 mm Hg compared to placebo, at 22-24 hours post-dosing).

Amlodipine + 20 mg – (additional reduction in systolic blood pressure of 2-9 mmHg compared to placebo).

4. Interaction with **alcohol** was studied at both the 10 mg and 20 mg dosage strengths.

Alcohol + 10 mg (Study LVAE) –

- Decrease in mean standing blood pressure was largest in the tadalafil + alcohol group.
- Increases in heart rate were greatest following co-administration of tadalafil + alcohol.
- Overall incidence of AEs was highest following co-administration of tadalafil + alcohol.
- Clinically significant blood pressure changes accompanied by symptoms only occurred in the tadalafil + alcohol group.
- Following alcohol +tadalafil, there were trends in greater impairment of postural stability and word recognition compared to alcohol +placebo.
- Slight impairment of saccadic eye movements occurred following alcohol +tadalafil compared to alcohol +placebo.

Reviewer's comment: By all metrics in this study, there appears to be an interaction between tadalafil 10 mg and alcohol, although the interaction does not appear to be life-threatening. The sponsor does not acknowledge such an interaction.

Alcohol + 20 mg (Study LVDO)–

In this larger study, there was no evidence of an interaction. In this study, serum ethanol levels were not measured.

Reviewer's comment: The discordant results between the 10 mg and 20 mg studies cannot be explained. Until they are explained, this reviewer considers this issue a significant NDA deficiency.

5. Interaction with **nitrates** (isosorbide dinitrate and sublingual nitroglycerin) was studied at only the 10 mg dosage strength.

Short-acting nitrates + tadalafil 10 mg (Study LVAB)

- a. The direct blood pressure lowering effect of tadalafil alone is small (approximately 3-4 mm Hg systolic pressure).
- b. The reduction in mean systolic blood pressure after sublingual NTG was 18 mm Hg when taken with placebo and 20 mm Hg when taken with tadalafil.
- c. The percentages of subjects who “survived” an entire, graded, infusion of intravenous NTG was 36%, 27%, 10%, and 9% for multiple-dose placebo, for single-dose tadalafil, for multiple-dose tadalafil, and for multiple-dose sildenafil (50 mg), respectively.

Reviewer’s comments

1. Despite design flaws, these studies still demonstrate the expected potential serious interaction with nitrates that requires a contraindication. Based on these results, the sponsor chose to exclude all nitrate users from Phase 3 studies.
2. **These studies were conducted with 10 mg tadalafil only.** Extrapolation to 20 mg is not possible.
3. **These studies enrolled only those patients who could tolerate a nitrate at baseline.**
4. An outlier analysis was not provided to me for Study LVAB.
5. These studies only investigated a single administration of NTG at a single timepoint. We do not know when the interaction with intravenous nitroglycerin will “wear off”. This is considered critical in the management of patients who have chest pain after taking tadalafil. In my view, such information is critical to the public health and constitutes a major NDA deficiency.

Short-acting nitrates + tadalafil 10 mg (Study LVCM)

A similar number of subjects had clinically significant changes in standing systolic and diastolic BP following administration of sublingual nitrate + tadalafil as compared to nitrate + sildenafil. The frequency in both groups was 2-fold higher than in the nitrate + placebo group.

Reviewer’s comment: Despite early assertions that Cialis had less of an interaction with nitrates than sildenafil, this doesn’t seem to be the case.

5.2 Biometrics

Ultimately, the statistician held that:

“It is evident from the sponsor’s analyses of these six trials that statistical significance between tadalafil groups and placebo has been achieved for 10 mg and 20 mg.”

He also noted that:

“Clinically relevant effect is essentially the same for 10 mg and 20 mg”. Evidence is weaker for 5 mg. **Pooling of the appropriate trials by this reviewer indicate no statistically persuasive evidence that 20 mg is more efficacious than 10 mg.**”

Dr. Hoberman conducted some additional analyses and provided some comments:

1. Dr. Hoberman found that the outcome of treatment with Cialis was “bimodal” in the sense that the majority of patients either **never** get a meaningful response, or that they **responded every month** for the duration of the three month trial. If a patient responded in the first month, he had a high probability of responding in all three months. These findings held true for all studies except LVCO (Taiwan).
2. Dr. Hoberman found that performance during the 4-week no-treatment baseline period played a significant role in a given patient fitting this “bimodal” responder paradigm.

For example, if a given patient had absolutely no successes during the baseline period, he would fit into the bimodal paradigm in that he could expect either to be a “responder” or a “non-responder”, but not an “intermittent responder”. To illustrate, in Studies LVDJ, LVCO, LVBK, and LVCQ, where 20 mg was studied, of those who had no successes at baseline, 31%, 16%, 27%, and 27% had no successes in the three-month treatment period on 20 mg. These rates of “no-success” in the “no-success at baseline” group were slightly higher for 10 mg (38% in LVDJ and 38% in LVBK).

If a given patient had at least one successful attempt in the baseline period, then the majority of those patients responded for all three months.

3. Dr. Hoberman notes that the performance of the 20 mg dose in LVBK (Spain) was below that in other trials. It is notable that this was the diabetics-only trial, exposure is lower in diabetics, and this finding may reveal a **lesser therapeutic benefit in diabetics**.
4. Dr. Hoberman notes that in the 6-month, placebo-controlled study, LVCQ (Australia), if a responder is defined as someone with at least 50% successes in each month, then the success rate was 85% for 20 mg and 47% in the placebo group.
5. Dr. Hoberman comments that if the label conveyed a single “timepoint” purporting to characterize _____ it would be misleading. The only potential true statement could be that approximately 65% of patients in the study attained at least one erection out of 4 attempts within 30 minutes of dosing.

Reviewer’s comment: I agree that no true, clinically meaningful, and accurate characterization of _____ can be made based on these results and no labeling claim should ultimately be allowed from this data.

6. Dr. Hoberman made several comments relevant to the _____ study LVDG. On this, ultimately, he held that differences could be distinguished between drug and placebo groups at 24 and 36 hours but that the terms _____ and _____ were misleading in the context of the design and results of this trial.

Reviewer’s comment: I agree that the sponsor should not be able to make claims about _____ based on these results since the design of LVDG did not allow for such claims. However, I believe that some part of these results may ultimately be presented in the label in an objective and descriptive manner.

5.3 Toxicology

The toxicologist ultimately held that:

“The preclinical studies conducted support the safety of the proposed dose of 20 mg of Cialis.”

Issues of note in Dr. Shin’s review included:

1. One of the major findings of treatment with Cialis in repeated dose (pre-clinical) studies was **arteritis** observed in multiple species. Dr. Shin said in her review that these major findings were “like other PDE5 inhibitors”.

Reviewer’s comment: In regard to the pre-clinical finding of arteritis and tadalafil, this reviewer remains concerned about the small margin of safety calculated for humans, the potential clinical relevance to humans, and the inadequate efforts made to diagnose arteritis in humans.

For tadalafil, Drs Shin and Jordan noted that vasculitis was observed in the mouse, rat and dog. Of greatest relevance, “disseminated arteritis was seen with increased incidence at high doses in the 1- and 6-month (dog) studies at exposures at a NOAEL for the unbound parent drug that **produce 2-fold, and 3 to 33-fold the human exposure at 20 mg, respectively.**” While recommending that these findings be included in the label, Drs. Shin and Jordan nevertheless provided several reasons for interpreting the data “cautiously”:

1. The pathogenic mechanisms of drug-related vascular lesions in animals are poorly understood.
2. The relevance to humans is poorly understood.
3. There was no evidence of epicardial hemorrhage or of medical necrosis in animals.
4. The lesions were not confined to the coronary arteries in animals.
5. Arteritis findings did not progress in the 1-year dog study.
6. The most commonly reported adverse events in humans did not include skin disorders as might be expected in human vasculitides.
7. The adverse events back pain and myalgia appeared to decrease in incidence with the use of concomitant anti-hypertensives and these might be expected to increase if back pain and myalgia represented latent vasculitis and drug-related hypotension is related to the development of vasculitis.
8. There was one study in humans (DSD06) measuring ESR and CPK without obvious drug effect on either biomarker of latent inflammation.

Reviewer’s comment: Drs Shin and Jordan recommending labeling these findings. This, coupled with their review comments, evoked concern for humans.

I have been provided no good evidence or rationale to refute the potential relevance to humans of this pre-clinical finding. The findings were noted at exposures as low as 2-fold human proposed exposure (at 20 mg). I have no explanation for the clinical adverse events “myalgia” and “back pain”. These events appear to increase with increased exposure and may be associated with long-lasting tadalafil metabolites. Tadalafil and its metabolites are of themselves long-lasting. Thus, overall, I believe that this is an NDA deficiency that impacts on assessment of human risk.

Dr. Shin states that these findings are "like other PDE inhibitors". However, I question the degree to which these events are similar across a drug class. The Division of Cardio-Renal Drug Products (DCRDP) commented upon these findings for sildenafil in a memo dated September 15, 1998. Drs. Papoian, DeFelice and Lipicky of the DCRDP stated that they made a deliberate and considered decision NOT to include arteritis in the labeling for Viagra. This was due to the fact (among other things) that plasma levels in dogs when administered the lowest dose that produced arteritis were 49X the maximum human therapeutic dose of 100 mg. Plasma levels in dogs at the no observable adverse effect level were 8X human exposure. Plasma levels in rats at the NOAEL were 3-7X human exposure. Plasma levels in rats when administered the lowest dose that produced arteritis were 19-29X the human exposure. Other issues that impacted on their decision NOT to label this preclinical finding included: 1) the potential for these lesions to reflect exaggerated continuous pharmacological effect of Viagra, and 2) pre-existing background disease in dogs. The review concluded that:

"the likelihood that such effects may occur in patients taking Viagra appears to be **minimal** given the fact that the human exposure is much lower than the exposure that produced arteritis in dogs or rats."

The memo also commented that:

"...determination of appropriate safety margins for human use should be based on the difference between the systemic exposure that produced the toxicity in animals and the systemic exposure in humans at the therapeutic dose, as well as the relative treatment conditions (chronic continuous exposure in animals versus the intermittent use in humans.)"

And further,

"Findings of arteritis in any species should be taken seriously."

And,

"There is no question that findings of arteritis in dogs were a clinical concern."

But the memo concludes,

"Substantial effort was made in the review to determine a safety margin."

And,

"The animal toxicity findings with sildenafil were not considered relevant to humans based on the higher doses and exposures required to produce the effects in animals, the longer duration of use in animal studies relative to human administration, and the possible unique sensitivity of arteritis in the dog and therefore, were not considered appropriate for labeling."

2. In terms of **testicular toxicity**, Dr. Shin described irreversible testicular degeneration/atrophy in the 3-month and carcinogenicity studies in mice and in the 3-, 6-, and 12-month toxicity studies in dogs with "no/low safety margin at the proposed human dose of 20 mg."

Reviewer's comment: Human studies assessing the effect of daily dosing of 10 mg (LVCD) and 20 mg (LVCZ) revealed no clinically relevant effect of Cialis on the human ejaculate with particular attention to sperm concentration, motility, and morphology.

3. Dr. Shin's review comments that "the 2-year carcinogenicity studies in male rats, and male and female mice were conducted at doses below those recommended by the ICH guidelines based on the AUC exposures for the 20 mg human dose." Dr. Shin says that the sponsor went ahead with these studies in mice and in rats without prior review of dose selection by the CAC. The "AUC ratio" for the unbound parent drug was only about 10-fold in both sexes in mice in the high-dose group, given a human dose of 20 mg. The "AUC ratio" in male rats was only 14-fold. The optimal ratio would be 25-fold.

In order to overcome this deficiency, the Committee (the CAC) recommended an alternative mouse carcinogenicity assay be conducted as a Phase 4 commitment unless the sponsor could provide evidence for "saturation of absorption" by measuring either total radioactivity or metabolites. On February 6, 2002, DRUDP informed the sponsor that they "strongly recommended" that Lilly conduct a study using radioactive drug to demonstrate saturation of absorption and that these studies should be conducted and submitted prior to the goal date. If absorption of saturation was not demonstrated in these studies, then a Phase 4 commitment to conduct an alternative assay would be required.

The sponsor pursued the conduct of such a study and submitted results of that study during the week of April 8-15. Dr. Jordan informs me that he has personally reviewed these results and he finds that they are acceptable. A Phase 4 commitment is not required.

Reviewer's comment: I remain concerned about the lack of adequate safety margin for humans (at 20 mg) for the finding of arteritis in the dog. This concern is heightened by the lack of an explanation for the adverse events of "myalgia" and "back pain". In my opinion, this toxicology finding remains a potential signal of clinical risk until additional efforts are made to explain the myalgias and back pain.

5.4 Chemistry

The chemistry reviewer finds the NDA to be "approvable".

Of note, there is a single manufacturing site in Indiana (Eli Lilly) for which the final recommendation from Office of Compliance is still pending.

I have recently discussed all potential outstanding issues with Drs. Rhee and Agarwal. I was told that other than the final Compliance recommendation, all other matters were resolved. I was informed that the sponsor accepted the restricted expiry date of \sim months for the 20 mg tablet. I was told that all deficiencies noted in the last IR letter to sponsor were satisfactorily addressed in the most recent response-to-IR letter, including all drug product and drug substance specifications (e.g. impurities). I was present at the OCPB Briefing on April 8, 2002, at which time OCPB agreed to accept the sponsor's proposed dissolution specifications. Dr. Agarwal agreed as well.

However, in his executive summary, Dr. Agarwal states the following concerns:

1. Adequate information for drug substance reference standards was not provided.
2. The system suitability of the analytical methods needs to be provided.

3. The sponsor must submit the required USP test results on the _____ that store the drug substance.

Apparently, Dr. Agarwal has written a "second review" and it is being signed off. These issues may be resolved in this "second review" but I have not yet been afforded this review. Dr. Agarwal informs me verbally that the "second review" resolves all these three issues.

Reviewer's comment: Other than the pending recommendation from Compliance re: the single manufacturing site, to my knowledge, all chemistry issues are resolved.

5.5 Division of Scientific Investigation (DSI)

Four pivotal studies investigated the 20 mg dose. One of these was in Spain (LVBK), one was in Australia (LVCQ), and one was in Taiwan (LVCO). Due to limitations on resources, DSI did not carry out international routine inspections for this NDA and therefore only Study LV DJ was inspected.

Pivotal study LV DJ was conducted in Canada. Therefore, the Division requested and DSI agreed to carry out inspections of two Canadian sites from pivotal Study LV DJ. For the routine inspections, _____ sites were inspected.

_____ enrolled 25 patients and there were no limitations on the inspection of his site. A Form 483 was not issued, however, there were some minor protocol violations. These included patient visits made outside the required time frame and a required ECG not being done. _____ enrolled 24 patients and there were no limitations on the inspection of his site. A Form 483 was not issued.

DSI concluded that the data submitted from these two sites appeared acceptable for supported this NDA.

Reviewer's comment: Without site inspections from Studies LVBK, LVCQ, and LVCO, it is impossible to assure reliability of that data. In my view, this is particularly important given the relative low incidences of adverse events in the Taiwan and Spain studies. I recommend routine inspections of each of the three outstanding trials.

5.5 Division of Anti-Inflammatory, Analgesic and Ophthalmological Drug Products (DAAOP)

Based upon the drug class and the potential for effects on retinal function, the sponsor carried out two special safety studies designed to investigate the effect of Cialis on vision. The reader is referred to Dr. Chambers' consultation report concerning the design and procedures for these studies, identified as LVAN and LV CN.

Reviewer's comment: Dr. Chambers opined that both studies were so flawed as to provide little useful data and so he recommended "class labeling and a Phase 4 commitment to conduct vision studies". This is a deficiency that should be conveyed to sponsor.

5.6 Division of Cardio-Renal Drug Products (DCRDP)

Based upon the finding of at least one unexplained sudden death in this NDA, syncopal episodes and myocardial infarctions in a few patients, the potential for phosphodiesterase inhibitors to affect the heart, and previous experience with other phosphodiesterase inhibitors, DCRDP was asked to review all material relevant to an assessment of the QT interval.

In pre-clinical studies, tadalafil (like sildenafil) blocked HERG I_{Kr} channels, but at concentrations far higher than typical plasma concentrations. There was no evidence of QT prolongation in beagle dogs given very high doses of tadalafil.

For humans, the sponsor submitted the results from eight studies in 7 protocols (see Dr. Stockbridge's review, Table 1). Each of these studies had EKGs done at several hours after dosing. There appeared to be no effect of tadalafil (at dose of 2.5 mg to 40 mg) on heart rate. In only two of these studies was a placebo employed and relevant EKGs conducted for assessment of QTc. In those two studies, there did not appear to be a relationship between dose and QTc at doses up to 40 mg. However, Dr. Stockbridge made several conclusions:

1. Submitted Study LVBS could provide even better information than the others due to the high dose studied (500 mg) and the intensity of monitoring.
2. There was no active control arm in these studies, making them less than optimal in design.
3. The observed variation in QTc makes it impossible to rule out a "clinically significant, even substantial" treatment effect.
4. The highest dose studied was only twice the apparent expected clinical dose. Dr. Stockbridge states "this is not a comforting safety margin".
5. Dr. Stockbridge questions whether there are any "electrophysiologically" active, longer-acting metabolites (e.g. the methylcatechol glucuronide).
6. Dr. Stockbridge comments on several syncopal cases from the ISS (all on active treatment) and recommends scrutiny of these cases and any available EKG data from them.
7. Dr. Stockbridge notes that there was only one sudden death in the NDA and overall "fewer deaths on active treatment than on placebo" and "fewer than might be expected in an elderly population with vascular disease."
8. Dr. Stockbridge states that "in short, then, the available data are clean, but not particularly reassuring."

Reviewer's comments:

1. In my opinion, the assessment of the QT interval was not adequate, based upon inadequate dose used and inadequate number of subjects enrolled into the relevant studies. In addition, there has not been an adequate assessment of metabolite potential for QT prolonging effect. In my opinion, this is a major deficiency.
2. **I agree with Dr. Stockbridge that the number of deaths was fewer than would be expected in this population. I am unable to explain the reason for so few deaths and serious adverse events. Some reasons might include inadequate collection of safety data, healthier population than U.S. ED population, and relatively small safety database, among others. The sponsor should be asked to explain this finding.**
3. **I agree that the syncopal cases (and other relevant cardiovascular events including myocardial infarction, angina, sudden death, and cerebrovascular accident) should be intensely scrutinized. Many of these events have been conscientiously scrutinized both by FDA and by sponsor. In my view, the real question is this: what sorts of data**

would be necessary to draw conclusions about drug attribution for these cases? Right now, the data submitted is not adequate to rule out a direct effect of drug but neither does it point to drug in a causative role.

I believe that the sponsor should be asked to defend cardiovascular safety by submitting all relevant results from new QTc studies, the stress test protocol, the coronary blood flow/PET scan protocol, and a review of all clinical CV adverse event data. This should be consulted to the Cardio-Renal Division and perhaps, shared with a Cardio-Renal Advisory Committee, if considered appropriate by the Cardio-Renal Division.

5.6 Financial Disclosure

Ms. Best's review stated that the financial certification information submitted on June 28, 2001, was adequate to "comply" with 21 CFR 54. She stated that the "rate of return of financial disclosure documentation" was acceptable. She stated that "the two investigators that reported disclosable information did not enroll a majority of patients at their sites, and therefore, it is unlikely that the outcomes of the trials was biased."

I reviewed the information on those two investigators as follows:

1. In Study LVBK (Spain) _____

2. In Study LVDJ (Canada) and Study LVCE (Canada), _____

Reviewer's comment: Therefore, I concur with Ms. Best's assessments that financial disclosure is not an outstanding issue here.

5.7 Pediatrics

Erectile dysfunction is a disorder of adult men only.

Reviewer's comment: A pediatric waiver would be appropriate at the time of drug approval.

6. Regulatory summary

I believe that this NDA should not be approved at this time. I have summarized my overall opinions and rationale for these opinions in the executive summary at the start of the memo and in various reviewer's comments throughout the memo.

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

/s/

Mark S. Hirsch
4/26/02 02:43:19 PM
MEDICAL OFFICER

Daniel A. Shames
4/29/02 03:34:28 PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 26, 2002

TIME: 1:00 – 2:30 pm

LOCATION: Parklawn Building, Rm. 13B-45

APPLICATION: NDA 21-368; Cialis (tadalafil) Tablets

TYPE OF MEETING: Discussion of application deficiencies

MEETING CHAIR: Florence Houn, M.D., Director, Office of Drug Evaluation III

MEETING RECORDER: Bronwyn Collier, B.S.N., Ass. Director for Regulatory Affairs, Office of Drug Evaluation III

FDA ATTENDEES

Office of Drug Evaluation III

Florence Houn, M.D., Director

Bronwyn Collier, B.S.N., Associate Director for Regulatory Affairs

Division of Reproductive and Urologic Drug Products

Daniel Shames, M.D., Acting Director

Dena Hixon, M.D., Acting Deputy Director

EXTERNAL CONSTITUENT ATTENDEES

Lilly ICOS LLC

Tim Franson, M.D.; Vice President, Clinical Research/Regulatory Affairs; Lilly

Jen Stotka, M.D.; Executive Director, US Regulatory Affairs; Lilly

Greg Brophy, PH.D.; Director, US Regulatory Affairs; Lilly

Charles Beasley, M.D.; Clinical Research Fellow, Medical Director; Lilly

Jeff Emmick, M.D., Ph.D.; Clinical Research Physician; Lilly

Cathy Melfi, Ph.D.; Regulatory Scientist, US Regulatory Affairs; Lilly

Ken Ferguson, Ph.D.; Chief Scientific Officer, Product Team COO; ICOS

Susan Sullivan, B.S.; Manager, Regulatory Affairs; ICOS

Consultants

[Redacted area]

BACKGROUND: NDA 21-368 for Cialis is under review in the Division of Reproductive and Urologic Drug Products (DRUDP). The proposed indication is treatment of erectile dysfunction at a dose of 20 mg. Several safety concerns were conveyed by DRUDP to Lilly ICOS on April 23, 2002. These concerns and Lilly ICOS' issues regarding communication with DRUDP were further discussed on April 24, 2002, in a telephone conversation between representatives from Lilly ICOS and Dr. Houn. Lilly ICOS requested this meeting to discuss the potential application deficiencies in greater detail.

DISCUSSION

Cialis-nitrate drug interaction

Lilly ICOS: Nitrate interaction studies conducted with tadalafil indicate that there is no residual interaction in the supine position when sublingual nitroglycerin is administered 26 hours after tadalafil 10 mg. Labeling Cialis with a contraindication for nitrate use is appropriate and acceptable. Additional information that will be available include:

- A 20mg/nitrate interaction study that will follow patients out to 72 hours. The protocol has been submitted to the IRB for approval but enrollment in this study has not been initiated yet.
- A study report of drug and stress testing in patients with coronary artery disease is complete and can be submitted to the NDA.
- **FDA:** There will be some men who experience chest pain following use of Cialis. Standard clinical practice is to treat chest pain with nitrates. Nitrates will likely be given in some of these cases, even if there is a stated contraindication in the Cialis labeling. Moreover, the drug's half-life is long and data indicate that there are effects of the drug on standing blood pressure. To provide complete information in the labeling, sufficient data is needed on nitrate-Cialis effects on blood pressure with the 20 mg dose or higher.

Potential for QTc prolongation

Lilly ICOS: Data do not show any effect on QTc with doses of Tadalafil up to 40 mg. A modest change in QTc is seen only at very high doses of Tadalafil. Tadalafil appears to be less potent in relation to effects on QTc than sildenafil. In addition, there is a phase 2 study (n=253) with daily dosing x21 days of Tadalafil 100 mg in 43 of the patients that suggests no effect. The data for this study were included in the NDA but a formal analysis was not. The formal analysis could be submitted within two weeks.

FDA: Effects on QTc may not have been detected because of inadequate dosing (i.e., the 40 mg dose used was not high enough). Effects on QTc could be further complicated by concomitant use of protease inhibitors and decreased drug clearance in special patient populations such as the elderly, and patients with renal and hepatic failure. The analysis of data from the phase 2 study that included a 100 mg. dose may be helpful in addressing this concern. If not, a clinical study may need to be performed to rule out QT effect.

Cialis-Alcohol interaction

Lilly ICOS: The 10 mg tadalafil/alcohol study showed a decrease in standing diastolic blood pressure. No similar blood pressure change was seen in the 20 mg tadalafil/alcohol study. No relationship between hypotensive adverse events or blood pressure decrements and alcohol consumption was seen in Phase 3 studies. It is unclear why the 10 and 20 mg studies results were contradictory. The following is proposed to address this concern:

- Adverse event and blood pressure by alcohol consumption analyses. These analyses could be submitted within 1-2 weeks.
- Conduct a new 20 mg alcohol hemodynamic study to replicate the original findings.

FDA: Information on the rapidity of the potential fall in blood pressure would be helpful to interpret overall study results (e.g., a slow decrease in blood pressure may allow time for the individual to compensate and a rapid decrease may be a greater safety concern). Information from the phase 3 studies is helpful but repeating the 20 mg study using 0.7 g/kg dose of alcohol and monitoring serum levels of alcohol and tadalafil is recommended to definitively address the current discrepancy in data.

Miscellaneous concerns

Manufacturing facilities: CDER's Division of Manufacturing and Product Quality will forward their recommendation regarding adequacy of the manufacturing facilities to DRUDP by April 29, 2002.

Back pain/myalgia: The etiology of the back pain and myalgias associated with Cialis use remains unclear. These events seem to be dose related. Monitoring and workup of these events in future studies of the drug in higher doses may provide useful information.

Drug-drug interactions: Additional information is needed on interactions between Cialis at all potential labeled doses (5-10-20 mg) and ketoconazole 400 mg, protease inhibitors, aspirin, and warfarin.

Dose: Efficacy information is available on Cialis 5, 10, and 20 mg. but the NDA proposes 20 mg as the optimal dose to minimize "failure" of erectile dysfunction treatment. However, safety concerns have led FDA to consider the lower doses and a possible titration regimen for dosing. Data submitted to address current gaps in information will further help determine whether a lower dose is more appropriate when interactions with other drugs or substances is likely to occur. Lilly ICOS representatives stated that if all doses are approved, they will probably market the 5 and 20 mg. tablets to provide the greatest flexibility.

Communications

Despite provision of comments by DRUDP on submitted protocols (e.g., drug interaction studies, phase 3) there are deficiencies in the scope of data included in the NDA. Inadequacies in communication could be due to a change in the direction of drug development (i.e., early development seems to target doses of 5 and 10 mg while phase 3 development includes the 20 mg dose), misunderstanding of the overall goals for drug development (e.g., one dose for every

man, focus on spontaneity as a clinical benefit), and changes in safety experience with other drugs for treatment of erectile dysfunction. .

CONCLUSIONS

- Alcohol interaction, effects on QTc, nitrate interaction, and cGMP issues (manufacturing facility) are probable areas that will need to be addressed before application approval.
- Nitrate interaction is a concern for all drugs similar to Cialis. ~~_____~~
- The action letter will state the deficiencies and may suggest a course of action to address the deficiencies. However, these suggestions do not limit the approaches that may be taken to address the need for more information.

ACTION ITEMS:

- An action letter, signed by Dr. Houn, will issue April 29, 2002, that details the information needed to approve the Cialis application.
- Lilly ICOS should include the new information and analyses discussed in the resubmission of the application.
- DRUDP will schedule a meeting to discuss the content of the resubmission.

Minutes Preparer: *See appended electronic signature page.*
Bronwyn Collier, B.S.N.
Associate Director for Regulatory Affairs
Office of Drug Evaluation III

Chair Concurrence: *See appended electronic signature page.*
Florence Houn, M.D.
Director
Office of Drug Evaluation III

MEETING MINUTES

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

/s/

Florence Houn
5/16/02 09:42:20 AM

Internal Meeting Minutes

Date: March 21, 2002 **Time:** 2:30 pm-4: 00 p.m. **Location:** Parklawn; 17B-43

Drug: Cialis

Sponsor: Lilly ICOS

Indication: erectile dysfunction

Type of Meeting: 9.5-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)

Shelley Slaughter, M.D., Ph.D., Acting Director, (DRUDP; HFD-580)

Wiley Chambers, M.D., Medical Team Leader, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAODP; HFD-550)

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)

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

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

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

Sandip Roy, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer (OCPB)

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

Barbara Chong, Supervisory Regulatory Review Officer, Division of Drug Marketing, Advertising, and Communications (DDMAC-HFD-42)

Cheryl Cropp, Pharm.D., Regulatory Review Officer, DDMAC, (HFD-42)

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

Meeting Objectives: To discuss the review of Cialis

Background:

Cialis (tadalafil) is a selective and potent inhibitor of the GMP-specific phosphodiesterase PDE5. This application was filed August 28, 2001. The PDUFA 10-month user fee goal date is April 29, 2002. The sponsor seeks approval of a 20 mg tablet

Discussion:

Action packet and Review due dates:

Medical Team Leader - March 25, 2002

Director - April 8, 2002

Office Director - April 15, 2002

Clinical Pharmacology and Biopharmaceutics:

- a draft review has been revised by the team leader and returned to the primary reviewer
- based on pharmacokinetic and pharmacodynamic analysis, the 10 mg dose is beneficial in most patients; some very small additional effect is found with the 20 mg in patients with severe erectile dysfunction
- patients diagnosed with severe renal insufficiency should be contraindicated from taking Cialis, patients with mild and moderate renal insufficiency have increased exposure compared to normals which appears to result in increased incidence of back pain
- an increase incidence in exposure and in incidence of back pain was demonstrated in the elderly (≥ 65 years)
- conclusions regarding drug interaction (e.g., amlodopine, alcohol, nitrate and theophylline in particular) will be based on clinical significance
- the overall recommendation is that the application is acceptable; the 10 mg dose should be recommended for any degree of renal impairment and patients over 65 years of age
- the reviewer notes that the methyl catechol glucuronide metabolite appears to "re-circulate" in the elderly and in the renally impaired
- the biopharmaceutics briefing is scheduled for April 8, 2002; the review will be finalized shortly after the briefing

Chemistry:

- the 20 mg strength is acceptable, review is completed
- the response to the information request sent to the sponsor February 11, 2002, and received March 6, 2002, is still under review; further clarifications requested from the sponsor
- the 10 mg strength is acceptable, no deficiencies
- DMF reviews are completed
- one Manufacturing site (Eli Lilly) inspection for drug substance and drug product is pending
- the 24 month expiration date requested by the sponsor is not acceptable, ~~24~~ -month expiration date will be granted
- dissolution acceptance is pending with the biopharmaceutics reviewer; final decisions regarding dissolution will be made at the OCPB briefing April 8, 2002

PharmTox:

- final draft review is with the Team Leader
- recommend addressing vasculitis in the label via a statement in the Pre-clinical studies section stating that, "relevance to humans is not understood but a margin of safety is 3-30 times"
- based upon CAC recommendations, a study to identify the saturation of absorption is currently ongoing and will be provided by the sponsor in mid-April for review; the reviewer anticipates being able to review these results prior to the goal date
- no non approval issues at this time, recommend NDA approval; however, if radioactivity study results do not assure saturation of absorption, a Phase 4 commitment of alternative mouse assay will be requested

Ophthalmology

- the review of two ophthalmology studies demonstrated no differences between Cialis, Viagra, or Placebo; however, significant errors in the execution and reporting of the studies were noted; changes known to occur with Viagra were also found
- insufficient data is available with respect to Cialis' effect on visual function

- findings are not different than findings found in the review of ophthalmology studies for Viagra; therefore, Cialis label should be consistent with Viagra's label to address this class of drugs
- recommend Phase 4 studies to obtain long term data

Clinical

- the first draft review is completed and was given to the Team leader on March 19, 2002
- a 10 mg dose should be recommended as the starting dose
- the 10 mg and the 20 mg doses are effective
- there are no major safety concerns
- the Medical Teamleader questioned the number of reported adverse events and reported that number of AE's appear low compared to other drugs in this class
- the Medical officer reported the following:
 - the sperm study is negative
 - there is no evidence of QT prolongation given two times the exposure
 - the common adverse events include headache, dyspepsia, back pain, rhinitis, and flushing
 - the reviewer agrees with a contraindication for severe renal insufficiency
 - the etiology of back pain and myalgia is not known, there were two cases of increased SER rates
 - there does not appear to be a liver toxic drug effect
 - the Medical reviewer reported that the two nitrate studies conducted by the sponsor were flawed; participants were individuals who could tolerate nitrates; despite flaws, blood pressure lowering effect was seen at 30 hours after sublingual nitrate administration to some Cialis patients; the use of nitrates with Cialis is undetermined; unable to determine use of nitrates in a population that may need nitrates; the study did not address multidose effect
 - regarding alcohol use, hypotension was observed at the legal intoxication rate; the drug interaction effect was not clinically significant
 - effect of Cialis with amlodopine was not clinically significant
 - effect of Cialis with theophylline was not clinically significant
- the majority of drug-drug interaction studies were conducted using the 10 mg dose (although alcohol and amlodopine were studied with the 20 mg); clinical effect could be different using the 20 mg dose
- the NDA can be approved; adequate information is available to address the risks in the label, recommendations would include limiting dosage to 10 mg for the elderly and mild to moderate renal impaired, and contraindicate in severe renal impaired patients

Statistics:

- Draft review is with the Team Leader
- efficacy for the 20 mg dose has been demonstrated
- efficacy for the 10 mg has also been demonstrated
- ~~_____~~ should be removed from the label
- the ~~_____~~ labeling is misleading
- the studies the sponsor submitted to justify 20 mg over the 10 mg included studies that utilized both the 10 and 20 mg dose, from the review of these studies, the 20 mg is not supported to be better than the 10 mg to a statistical difference

DDMAC

- will review label and provide comments

DSI

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

/s/

Mark S. Hirsch
4/25/02 11:16:56 AM

Meeting Minutes

Date: March 7, 2002 **Time:** 10:00 am-11: 00 a.m. **Location:** Parklawn; 17B-43

Drug: Cialis

Sponsor: Lilly ICOS

Indication: erectile dysfunction

Type of Meeting: 9-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)

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

Rajiv Agarwal, Ph.D., Chemistry reviewer

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

Meeting Objectives: To discuss the review of Cialis

Background:

Cialis, Tadalafil, is a selective and potent inhibitor of the GMP-specific phosphodiesterase PDE5. A Pre-NDA meeting was held February 21, 2001; this application was dated June 28, 2001 and received June 29, 2001. The application was filed on August 28, 2001. The 10-month user fee goal date is April 29, 2002.

Discussion:

Clinical

- review is ongoing
- the 10 mg and the 20 mg doses are effective
- there are no major safety concerns discovered thus far during the review
- advice to health professionals regarding the timing at which nitroglycerine may be administered after taking Cialis is unknown given the drugs $\frac{1}{2}$ life of 17 hours; in the nitroglycerine infusions studies, NTG was administered at only one time point
- the Medical Team Leader reported that a teleconference was held with the sponsor on February 20, 2002, in which the sponsor was asked to provide the rationale not pursuing the 10 mg dose for market; this information was received today and will be reviewed; only two studies utilizing the 10 and 20 mg dose were provided to demonstrate efficacy above the 20 mg dose; statistics should evaluate the appropriate studies to confirm the differences in efficacy between the 10 mg and the 20 mg dose
- the draft clinical review will be provided to the Team Leader by March 11, 2002
- unexpected back pain was reported lasting up to "days" after dosing

- there was an interaction with alcohol in the 10 mg study
- both the ophthalmologist and Cardio-Renal consults are not yet completed

Statistics:

- final draft with Team Leader
- appropriate trials to demonstrate 20 mg efficacy over the 10 mg will be evaluated
- _____ of effect is an issue that should be addressed in the labeling
- instructions provided during Phase 3 trials will provide insight in recommending instructions for use
- regarding _____ the study is not considered supportive of labeling
- regarding current labeling for _____ the study is considered misleading

Chemistry:

- Chemistry review #1 is finalized and in DFS
- labeling comments are on the "N" drive
- a warning statement: "keep Cialis out of reach of children" is recommended for the container label
- inspection of the drug substance and drug product manufacturing facility (Eli-Lilly) is pending; the drug product manufacturing site is on withhold for another NDA
- a deficiency letter was sent to the sponsor on February 12, 2002 and there is no response yet from the sponsor

Clinical Pharmacology and Biopharmaceutics:

- a draft review is to go to the Team Leader in a few days
- the Office of Biopharmaceutics finds the application "acceptable" but recommends the addition of a 10 mg dose strength
- there appears to be a relationship between the methyl catechol metabolite and the incidence of back pain
- pharmacodynamic studies utilizing the 10 mg dose demonstrated a decrease in blood pressure with the administration of alcohol; clinical significance will be assessed by the medical officer
- exposure is approximately two-times expected for any degree of renal insufficiency
- OCPB briefing is scheduled for April 8, 2002

PharmTox:

- final review is with the Team Leader
- vasculitis has been identified in pre-clinical studies with beagle dogs, the margin of safety to human exposure is different in two different beagle dog studies (very large margin in N.Y. study, very small margin in England study)
- reviewer concludes that margin of safety for vasculitis finding in beagle dogs should be labeled as 3-33-times
- based on CAC recommendation that saturation of absorption was not assured for both parent and major metabolites, a teleconference was held with the sponsor on February 6, 2002, to discuss options; the sponsor could either conduct a new radioactivity study prior to goal date and submit results for review, or sponsor could do alternative mouse assay post-approval; the sponsor proposed to conduct the radioactivity study and the Division accepted the proposal; the study is ongoing and results will be submitted for review during this review cycle.
- label review is pending

DSI

- one inspection is pending

Action Items:

- a status meeting will be scheduled within the next 2 weeks

Date Completed

2/8/02

Next Meeting: March 21, 2002

Minutes Preparer:

Meeting Chair

cc:

Original NDA/21-368
HFD-580/Div. Files

Drafted by: Spell-LeSane, 4.2.02

Concurrence: Benson, Hirsch, Shin, 4.11.02/Agarwal, 4.24.02

final: Spell-LeSane, April 25, 2002

MEETING MINUTES

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

/s/

Mark S. Hirsch
4/25/02 11:08:48 AM

Food and Drug Administration
Rockville MD 20857

MAR - 7 2002

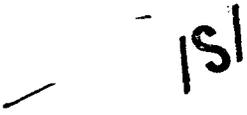
Dear Dr. _____

Between January 21 and 23, 2002, Ms. Diane C. Van Leeuwen, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol H6D-MC-LVDJ) of the investigational drug Cialis™ (tadalafil), performed for Lilly ICOS. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Van Leeuwen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I, by letter at the address given below.

Sincerely yours,


Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003510531

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-580 Doc.Rm. NDA# 21-368

HFD-580 Review Div.Dir. (Shames [acting])

HFD-580 MO (Batra)

HFD-580 PM (Spellesane)

HFD-45 Reading File

HFD-47 Chron File

HFD-47 GCP File #10568

HFD-47 GCP Reviewer (Blay)

HFD-47 CSO (Currier)

HFC-132 (Kadar)

HFR-PA250 Field Investigator (Van Leeuwen)

d:CAC:3/4/02

reviewed:AEH:(date)

f/t:mb:(date)

o:\cac:\o:\cac\ _____ .doc

Reviewer Note to Rev. Div. M.O.

Twenty-four subjects were enrolled in the study and 20 subjects completed. Four subjects discontinued, two withdrew consent, one had an early termination, and one was entered but was not randomized due to an AE (brain aneurysm). Ten of the 24 subjects' records were reviewed during the inspection, and no significant deficiencies were found. Informed consent forms for all 24 subjects were appropriately signed. It appears that the data reviewed during this inspection is acceptable for use in support of the NDA.

MEMORANDUM OF TELECON

DATE: March 15, 2002

Time: 4:25 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
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 that the sponsor be called to 1) request chemistry information and 2) provided the sponsor with carton labeling comments.

Discussion:

1. Please provide qualitative components and relevant reference to CFR regulations of the _____

Container Labeling comments:

1.

2.

3.

4.

5.

6.

[Redacted]

7.

[Redacted]

[Redacted]

8.

Decisions reached:

- sponsor will provide response to information requested and review recommendation for the carton labeling
- **Action Items:**
- Meeting minutes to be conveyed within 30 days

Dornette Spell-LeSane, MHA, RN, NP-C
Regulatory Project Manager

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

/s/

Dornette Spell-LeSane
4/13/02 04:39:05 PM
CSO

Dornette Spell-LeSane
4/13/02 04:48:06 PM
CSO



Mark A. Barbato
Executive Director and Team Leader Primary Care Products
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Food and Drug Administration
Rockville MD 20857

MAR - 1 2002

Dear Mr. Barbato:

Between January 7 and 14, 2002, Ms. Leigh A. Myers, representing the Food and Drug Administration (FDA), conducted an inspection of the monitoring practices of Lilly ICOS, LLC, for a clinical study (Protocal HGD-MC-LVDJ) of the investigational drug IC351 (LY45-190). This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections of sponsors/contract research organizations/monitors, designed to ensure the proper conduct of clinical studies for submission to the FDA, and to ensure that the rights and welfare of human subjects have been protected.

Based on our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the federal regulations governing sponsor/contract research organization/monitor responsibilities for the conduct of clinical studies and the protection of human subjects.

We appreciate the cooperation shown Investigator Myers during the inspection. Should you have any questions or concerns about clinical testing of investigational drugs, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I, in writing at the address below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branches I and II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN: 3003567845

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

cc:

HFA-224

HFD-580/Doc.Rm/NDA 21-368

HFD-580/Batra

HFD-580/Spell-Lesane

HFD-45/Reading File

HFD-46/Chron File

HFD-46/GCP File #010555

HFD-46/Blay

HFR-CE750/Dempster

HFR-CE750/Bellamy

HFR-CE750/Myers

r/d:CAC: 2/25/02

reviewed:/AEH:

reviewed:/rab:/2.28.02

f/t:sg: 3/1/02

o:\blay\lillyicos.doc

Reviewer Note to Review Division M.O.:

This sponsor inspection assignment was issued because NDA 21-368 is a 1-S drug. There were no problems found during the inspection that would invalidate the study data being submitted in support of NDA 21-368.

MEMORANDUM OF TELECON

DATE: February 20, 2002
Time: 3:30 p.m.
APPLICATION NUMBER: NDA 21-368, Cialis (tadalafil) tablet

BETWEEN:

Name:

From ICOS:

Steve Whitaker, M.D. Director, Clinical Research
Ken Ferguson, Ph.D. Chief Scientific Officer, Cialis Team
Jeff Hessesberg, M.A. Director, Regulatory
Susan Sullivan B.S. Sr. Manager, Regulatory

From Lilly:

Charles Beasley, M.D. Medical Director
Jeff Emmick, M.D., Ph.D. Clinical Research Physician
Vish Watkins, M.D. Clinical Research Physician
Mark Barbato, B.S., MBA Cialis Team Leader
Cathy Melfi, Ph.D. Regulatory Scientist

Phone:

317-433-5287

Representing:

Lilly ICOS LLC

AND

Name:

Dornette Spell-LeSane, NP-C, MHA,
Regulatory Project Manager
Mark Hirsch, M.D. Medical Team Leader
Ashok Batra, M.D. Medical Officer
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT:

Clinical discussion

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 Clinical Review Team requested a teleconference with the sponsor to discuss clinical issues for this pending application.

Discussion:

- reviews are ongoing
- the Division would like to discuss and obtain feedback on the sponsor's decision not to pursue the 10 mg dose

Rationale for not pursuing the 10 mg dose

- preliminary discussions among the Division's review team included questions regarding the sponsor's rationale for not pursuing the 10 mg dose; the Division would like the sponsor to provide their rationale for not pursuing the 10 mg dose
- the sponsor stated that it was their position that the 20 mg dose provided the optimal efficacy required for the disorder (erectile dysfunction) without the necessity for titration and to minimize failures; the sponsor stated that the 20 mg dose demonstrated superior efficacy to the 10 mg dose in head-to-head trials
- regarding safety, the sponsor stated that there were no differences in the discontinuation rate and few differences in individual adverse event rates and therefore they believe the doses have an equivalent safety profile

Issues related to not pursuing the 10 mg dose:

Issue #1: Drug effect on mild to moderate renal impaired patients

- DRUDP stated that the Clinical Pharmacology review team found that for the mild to moderate renally impaired patients drug exposure after the 10 mg dose is approximately two times the exposure for the non-renally impaired patients
- the sponsor stated that there are on-going studies addressing renal patients on dialysis, however, regarding the biopharm study mentioned, the non renal impaired patients or normal patients were "super clearers"; the findings for the mild to moderate group when compared to normal subjects is comparable; in addition, increased exposure have not been found with dialysis patients

Issue #2: Dose related effects on dyspepsia and myalgia

- DRUDP asked the sponsor if the findings of dyspepsia and myalgia were dose related because they appeared to be so
- the sponsor provided some statistics for the placebo, 10 mg, and 20 mg doses and concluded that there were minor differences between the 10 mg and 20 mg in relationship to documented events

Issue #3 Interaction with amlodopine

- DRUDP stated that in studies with amlodopine and the 10 mg dose where the endpoint is pharmacokinetics, pharmacodynamic effects for the 20 mg cannot be extrapolated
- the sponsor states that the 10 mg study was followed up by a study utilizing the 20 mg dose in the original submission for study LVDP; there was less of an effect between placebo and the 20 mg than between 10 mg and placebo

Issue #4: Interaction with alcohol

- DRUDP stated that in studies with alcohol and the 10 mg dose, there appeared to be an effect of Cialis on blood pressure and adverse events; in studies with alcohol and the 20 mg dose, the drug effect appeared less prominent; the sponsor was asked to interpret those results
- the sponsor stated that there was no alcohol interaction at 20 mg

Decisions reached:

- sponsor agreed to the following:
 - propose justification why there is no clinically meaningful interaction with alcohol
 - submit risk/benefit rationale in support of the 20 mg and reasoning for not pursuing the 10 mg
 - submit the additional clinical pharmacology data to support safety of the 20 mg dose
 - provide final safety update using brief narrative format by March 1, 2002