There was one sudden death without causal determination[4], but overall fewer deaths on active treatment than on placebo and fewer than might be expected in an elderly population with vascular disease.

In short, then, the available data are clean, but not particularly reassuring.

If the Division of Cardio-Renal Drug Products can be of further assistance in this matter, please let us know.

[4] *Subject LVBL 007-3072.*

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/s/

Norman Stockbridge
3/12/02 11:13:38 AM
MEDICAL OFFICER

Doug Throckmorton
3/12/02 12:24:30 PM
MEDICAL OFFICER

NDA 21-368

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

MEDICAL OFFICER REVIEW OF NDA 21-368 (DRAFT)

SPONSOR:	Eli-Lilly laboratories, Inc.
DRUG PRODUCT:	Cialis™ (IC351)
DOSE:	20 mg
ROUTE OF ADMINISTRATION:	ORAL
PHARMACOLOGICAL CLASS:	Phosphodiestrase V Inhibitor
INDICATION:	Male Erectile Dysfunction
DATES:	
SUBMITTED:	June 26, 2001
CDER STAMP:	June 28, 2001
PDUFA GOAL:	April 29, 2002
RELATED IND's:	*IND # 54553*
MEDICAL OFFICER	Ashok Batra, MD
DATE REVIEW COMPLETED:	April 05, 2002

Ashok Batra, MD
MEDICAL OFFICER

Mark Hirsch, MD
MEDICAL TEAM LEADER

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Executive Summary

1. Recommendations

1.1. Approvability

This reviewer is of the view that Cialis™ 20 mg be recommended for a NOT approvable action for the proposed indication of male erectile dysfunction. Some safety issues remain. There is insufficient data to assess risk regarding use of nitrates in IC 351 treated patients and its management. There is an increased risk in patients with renal compromise due to increased drug and metabolite exposure. This is associated with adverse events such as back pain and myalgia. The pathogenesis and mechanism of these is currently unknown. QTc data is inadequate if 20 mg dose is sought. There was a dose related increase in the trend in the common adverse events such as headache and dyspepsia. The data with 20 mg dose in few drug interactions is not submitted instead only 10 mg interaction data is extrapolated to 20 mg.

1.2. Basis for recommendation regarding approvability (risk/benefit assessment)

Benefits

Phosphodiesterases (PDEs) are enzymes that are present in various tissues with different functions, all ultimately act to hydrolyze cyclic nucleotides, thereby terminating their actions. There are eleven known phosphodiesterase classes identified so far, many with subtypes identified by structure and function. Phosphodiesterase type 5 (PDE5) is a major c-GMP-hydrolyzing enzyme in vascular smooth muscle of the penis.

IC351 (tadalafil) is a selective inhibitor of the cGMP-specific phosphodiesterase type 5 (PDE5) investigated for the treatment of Erectile Dysfunction (ED). Sexual stimulation causes the local release of nitric oxide with activation of guanylyl cyclase. IC351 inhibition of PDE5 produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and in flow of blood into the penile tissues, thereby producing an erection.

According to the sponsor, In vitro, IC351 was found to be >10,000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, and other organs. IC351 is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE 5 over PDE 3 is important because PDE3 is an enzyme involved in cardiac contractility.

Additionally, IC351 is approximately 700-fold more potent forPDE5than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. IC351 is also >10,000-fold more potent for PDE5 than for PDE7-10.

The pharmacokinetic profile of IC351 showed that it has a mean half-life of 17.5 hours and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 2 hours after dosing.

The sponsors conducted six, placebo-controlled, multi-center clinical studies in Argentina, Australia, Canada, Mexico, Spain, and Taiwan. One of these studies (LVBK) included only patients with diabetes mellitus. The time to onset of the period of responsiveness and the duration of the period of responsiveness were evaluated in studies conducted either wholly or partially in the United States (US).

Generally, the studies contained a similar number of patients of each demographic characteristic; Age, body mass index (BMI), smoking status, hypertension, heart disease, diabetes, depression, and ethnicity. These studies included a broad population of patients having all severities and etiologies of ED, and appeared to mimic the US population with ED except low numbers of patients of African descent (<1%). The primary placebo-controlled Phase 3 trials included 1328 patients with ED and the doses studied in these trials ranged from 2.5 mg to 20 mg IC351. Across all clinical trials, single doses of up to 500 mg IC351 and multiple daily doses up to 100 mg IC351 were administered to healthy subjects and/or patients with ED. As of March 2002, a total of approximately 500 patients were exposed to the proposed dose of 20 mg IC351 (or an equivalent [redacted]) for at least one year, and 800 patients have been exposed to 20 mg IC351 (or an equivalent [redacted]) for at least 6 months.

Each primary efficacy study had three co-primary endpoints: the International Index Of Erectile Function (IIEF), Erectile Function (EF) Domain, Sexual Encounter Profile (SEP) Question 2 (assessing the ability to penetrate the partner's vagina), and SEP Question 3 (assessing the ability to maintain the erection). All endpoints were analyzed as the change from baseline. The baseline and endpoint score for each SEP question is the patient's percentage of "yes" responses to that question during the run-in period (that is, the interval between Visit 1 and Visit 2) and the post baseline period, respectively. For any individual sexual encounter, if the patient answered "no" for any SEP question, subsequent questions were analyzed as "no" responses.

IC351 (2.5-20 mg) improved erectile function as measured by the IIEF EF Domain compared with placebo. Statistically significant improvement was observed at all doses except 2.5 mg IC351. The change from baseline for the 5 mg IC351 dose was from 4.0 to 5.1. Responses to 10 mg were 5.6 to 8.1. The 20 mg IC351 dose provided a response of around 8 points.

IC351 improved sexual performance as measured by SEP Question 2 (ability to penetrate the partner's vagina) compared with placebo. The 5-mg IC351 dose significantly improved the response to SEP Question 2 in only one (LVCE) of two studies. Generally, each dose demonstrated consistent change from baseline between

studies. In Phase III studies, the 10 mg IC351 dose provided a change in successful intercourse attempts in the range of 15.1 to 34.5, while 20 mg provided the change in the range of 21.3 to 35.3.
As measured by SEP Question 3, in all studies the overall percentage of successful intercourse attempts was similar between all treatment groups in the treatment-free run-in period. Also in all studies, IC351 improved the response to SEP Question 3 compared with placebo. All doses significantly improved patients' ability to maintain their erection for successful intercourse compared with placebo. Greater improvement was demonstrated with increasing dose. The percentage of successful intercourse attempts was slightly greater for the 20 mg IC351 treatment group in the range of 26.5 to 49.7 than for the 10 mg treatment group that was in the range of 25.8 to 47.9.

The integrated analysis of SEP Question 3 data demonstrates that 74.7% of all post baseline attempts were successful for 20 mg IC351, compared with 60.9% for 10 mg IC351 and 31.9% for placebo. Thus, both 10 and 20 mg doses achieved statistically and clinically meaningful improvement in the majority of ED patients.

Risks

All across the safety database headache, dyspepsia, back pain, myalgia, nasal congestion, and flushing were the most frequent adverse events (AEs) in the IC351-treated patients.
In the placebo-controlled, market image formulation, "at home" studies headache (11%), dyspepsia (7%), back pain (4%), myalgia (4%), nasal congestion (4%), and flushing (4%) were seen in the IC351-treated group. Adverse events were generally mild to moderate in intensity with some exceptions. The association of these events with IC351 as a PDE5 inhibitor is plausible. Dyspepsia is thought to result from relaxation of lower esophageal smooth muscle tone by inhibition of PDE5. Headache, nasal congestion, and flushing can all be due to vasodilatation. The mechanism and pathogenesis of back pain and myalgia is unknown. These latter two adverse events were particularly of note in the studies where the patients had mild to moderate renal failure because the incidence of these two AEs was significantly increased. This presents an unknown safety risk and may be due to the long sojourn of the drug in the body and the associated increased exposure to its metabolite.
In the primary placebo controlled Phase 3 database (N= 1,328), serious adverse events (SAEs) were reported by 15 patients. The incidence of SAEs was not statistically significantly different between treatment groups. In the IC351-treated group, 9 of 949 patients (0.9%) reported at least one serious adverse event compared with 6 of 379 (1.6%) of placebo-treated patients. There were no deaths reported during the primary placebo-controlled Phase 3 studies. As of the March 2002 safety update, 7 deaths occurred during clinical trials with IC351. However, review of the data did not establish an unequivocal direct causal relationship to the drug.
In the placebo-controlled Phase 3 studies, 27 patients (2.0%) discontinued due to adverse events, 5 of 379 patients (1.3%) in the placebo group and 22 of 949 patients (2.3%) in the IC351-treated group. *The discontinuation rate (3.6%) in the 20 mg group*

(N=330) was twice as much as the 1.5% rate in the 10 mg dose group (N=394). Discontinuations due to adverse events in three long-term, open-label studies (LVBD, LVBL, and LVDR) were 4.4%, 5.4% and 5.7 %, respectively.

Cardiovascular Safety

Nitrate interaction studies were performed (LVBY and LVCM). The IC351 10mg dose used in these studies was lower than the sought dose of 20mg. The sponsor was advised by the Cardiorenal Division in their pre-NDA discussions to use doses up to 80 mg for an adequate safety margin. IC 351 10mg augmented the hypotensive effects of nitrates. In these nitrate interaction studies, the greatest augmentation of the hypotensive effects of nitrates was typically seen within 4 hours of IC351 administration. There was approximately 20 mm (sysytolic) hypotension with nitrates alone, and a 2-5 mm of additional hypotensive effect with the use of Cialis™ 10 mg . This could be significant in some patients. Therefore, concomitant use of Cialis with nitrates should be contraindicated. Additional data/studies are needed to clearly outline the qualitative and quantitative hypotensive effect of nitrates and IC351 taken in combination for the entire duration of IC 351 exposure.
Based upon pre clinical and Phase 1 & 3 studies (with the maximum dose of 40 mg used) there was no clear signal to suggest that IC351 prolongs the QT interval. This safety margin used for the QTc studies is unacceptably low if 20 mg is the only dose sought by the sponsor. Additional data using 80 mg, four times the dose sought, will be required. Clinical pharmacology data showed that the incidence of combined events of dizziness, syncope, and postural hypotension were similar to the placebo population. These events could not be directly attributed to the drug. In the primary, placebo-controlled Phase 3 safety database, the incidence of flushing was 3.7% for all IC351-treated patients compared with 1.6% for placebo-treated patients. Dizziness occurred in 2.4% of patients taking IC351 compared with 1.9% of placebo-treated patients. Syncope occurred in 0.1% of patients taking IC351 compared with 0.5% of placebo-treated patients. Many of these events occurred in the two Nitrate interaction studies.

In the primary, placebo-controlled Phase 3 safety database, 3 patients suffered myocardial infarctions. Two events occurred in the placebo-group. The incidence rate of myocardial infarction in patients treated with IC351 was similar to the incidence rate (0.6 per 100 patient-years) observed in an age-standardized general male population. Nine myocardial infarctions (0.65%) were reported in the open label long-term studies.

Human Sperm Characteristics and Spermatogenesis
Studies LVCD and LVCZ were randomized, double-blind placebo-controlled 6-month studies to evaluate the effect of 10 mg (LVCD) and 20 mg IC351 (LVCZ) given daily on semen characteristics in healthy subjects and subjects with mild erectile dysfunction. These studies did not show clinically significant effects on multiple semen parameters with these doses.
Visual Safety

Phosphodiesterase inhibitors have the potential to affect visual function. The mechanism is believed to involve the inhibition of PDE6, an enzyme found in the retina and thought to be responsible for photo transduction.

The sponsors studied over 4000 subjects who took IC351 in clinical pharmacology, Phase 2, and Phase 3 studies. There were no dose-related visual symptoms, especially color tinge changes, with multiple doses of up to 100 mg IC351 given for 14 consecutive days and single doses up to 500 mg. There were three reports of abnormal color vision in the 4000 patients treated with IC351 (incidence rate <0.1%). The study population showed a very low incidence of visual abnormalities with this product. However, the FDA ophthalmology consultant did not find any difference in this product and another drug of its class (sildenafil) as far as the vision was concerned and recommended that the label should reflect that fact. Additional well-controlled studies were also recommended.

Laboratory Safety

In two early dog toxicity studies, histopathologic evaluation revealed evidence of vascular inflammation (arteritis) in dogs. These dogs were from a colony with a high incidence of Beagle Pain Syndrome (BPS), a spontaneous, idiopathic disease of beagles which is associated with arteritis. The toxicology review indicated an association of IC 351 with dog arteritis. Because of this finding and the adverse events of back pain and myalgia in the earlier human trials, the sponsor was asked to look at both ESR and CK lab values in IC 351-treated patients. There was no clinically significant elevation of these tests in subsequent human studies.

In a 12-month dog toxicity study, two dogs experienced decreases in blood cell counts (primarily neutropenia and thrombocytopenia). Of the 4000 subjects who received IC351, these findings were not seen and did not reach a level of clinical significance. Upon review of liver function tests, there was no indication that IC351 was associated with drug-induced hepatotoxicity.

Headache, dyspepsia, back pain, myalgia, nasal congestion, and flushing were the most commonly reported adverse events. However a dose related increase was seen in headache, flushing and dyspepsia categories in 20 mg group. Additionally in pivotal studies the discontinuation rate due to adverse events in the 20 mg group was more than double the rate in the 10 mg group.

1.3 Summary of Benefit / Risk (Including Dose-Response)

IC 351 has a long ½ life. Any compromise in renal function may increase the exposure to the drug or its metabolite. This presents an unknown safety risk in the form of adverse events such as back pain, myalgia and adverse events due to interaction with drugs that cause vasodilatation. A dose related increase was seen in headache, flushing and dyspepsia in the 20 mg group. Additionally, in pivotal studies the discontinuation rate due to adverse events in the 20 mg group was more than double

the rate in the 10 mg group. For the sponsor's proposed 20 mg dose the question of Nitrate interaction is still not answered and QTc data does not provide a comfortable safety margin. Limited interaction studies were done with 10 mg and extrapolated to 20 mg.

In the six pivotal studies, 10 mg and 20 mg showed clinical and statistical improvement in the parameters for ED. 5 mg was clinically efficacious in the large number of patients studied (n=151 in pivotal trials). Statistically, it showed significance in all primary endpoints except SEP 2 in one trial (p= .064). However, given the drug's long half-life and higher exposures in elderly and renal-compromised patients, this could be quite significant for 20 mg as the starting dose, as requested by the sponsor.

In summary, based on a thorough review of the safety and efficacy information contained in NDA 21-368, this reviewer believes that the sponsor has demonstrated that Cialis™ (5 mg, 10 mg and 20 mg) is effective for the proposed indication of treatment of male erectile dysfunction. The therapeutic risk/benefit index, however, does not support 20 mg for the starting dose at present due to safety concerns.

1.4. Specific recommendations to the sponsor

Male erectile dysfunction presents in a full spectrum from mild to severe dysfunction to no function. Occasionally this may present as a fluctuating and unstable disease particularly in ED patients of psychogenic etiology. Many men have relatively less severe forms. Future patients will benefit from 5 mg OR 10 mg as a starting dose with an option to titrate up if needed; alternatively, they will no choice, but to take 20 mg as an initial dose. This could be potentially dangerous for patients with decreasing renal function. Another reason for a lower starting dose is the incidence of dose-related increase in headache, vasodilatation and dyspepsia that may rise over time due to the potential for off-label high consumption of this drug. More information is required to understand the safe administration of nitrates in these patients. The QTc data does not have a wide enough safety margin for the proposed 20 mg dose. Additionally, the interaction studies done with 10mg IC 351 can not be extrapolated to the 20 mg dose, especially when the interaction is with another vasodilatory drug.

2. Summary of clinical findings

2.1. Brief overview of the clinical program

2.1.1 Drug product:

Name (INN): Tadalafil

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

Molecular weight : 389.41.

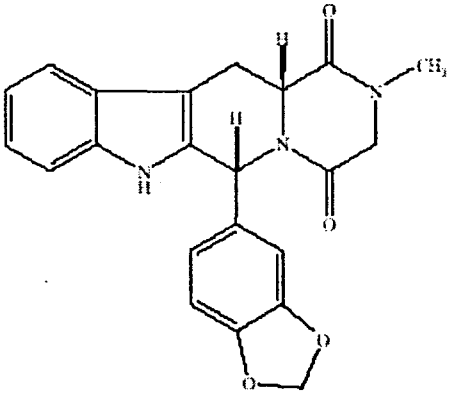
Proprietary (Brand) Name: Cialis

Synonyms: Beta Carboline Phosphodiesterase Type 5 Inhibitor, IC351

Solubility: Practically insoluble in water; very slightly soluble in ethanol;

Structural Formula:

Figure 1: (Structural Formula (Tadalafil))



CIALIS (tadalafil), an oral treatment for erectile dysfunction, is a potent, selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). It is manufactured by Eli Lilly and Company, Indianapolis, Indiana. Phase 3 clinical trials were conducted with material sourced from active ingredient manufactured at full scale by the commercial synthesis.
It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.
CIALIS is available as yellow, film-coated, almond-shaped tablets for oral administration. Each tablet contains 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

Tadalafil tablets are packaged into ——————— : blisters that are sealed with ——————— Tablets are blister packaged with one tablet per blister cavity. The individual blister cavities may be combined into strips or cards as appropriate for each market sector.

2.1.2. Brief overview of the clinical trials conducted

The sponsor submitted data from the following studies in support of NDA 21-368.

- 42 completed and 4 ongoing clinical pharmacology studies conducted with IC351, as well as the 4 studies that examined population pharmacokinetics and pharmacodynamics (LVAC, LVBF, LVBG, and LVCE).
- The safety of IC351 has been studied in clinical trials with over 4000 subjects and patients.
- Efficacy at various doses was evaluated in 16 clinical trials with over 2800 men with ED receiving active treatment. Early clinical trials evaluated various dosing regimens in terms of timing (daily or as needed), dose strength, and need for titration.
- Six primary adequate and well-controlled studies on which the efficacy and safety of IC351 in the treatment of ED is primarily based (LVBN, LVCE, LVCQ, LVCO, LVDJ, and LVBK).
- Three studies were conducted to examine the time to onset of response and period of responsiveness to IC351 so that appropriate dosing instructions could be determined. The sponsor conducted a placebo-controlled study in the US (LVCR). This was reviewed for safety.
- In addition to the open-label studies (LVBL, LVBD and LVDR) in which efficacy and safety were evaluated, safety assessment of IC351 also included 2 studies for changes in sperm parameters. In the open-label studies, patients received treatment with IC351 for up to 21 months.

2.2 Efficacy

2.2.1. Primary efficacy assessments and efficacy endpoints

Overview of Efficacy Measures

The sponsors used three instruments to assess efficacy in the six IC351 primary efficacy studies: the International Index of Erectile Function (IIEF), Sexual Encounter Profile (SEP) diaries, and Global Assessment Questions (GAQ). SEP diaries were used to evaluate the period of responsiveness. Each primary efficacy study had three co-primary variables:

- IIEF Erectile Function (EF) Domain
- SEP Question 2 (assessing the ability to penetrate the partner's vagina)
- SEP Question 3 (assessing the ability to maintain the erection)

The IIEF is a validated, multidimensional, self-administered questionnaire commonly employed to assess the effect of ED treatment. The IIEF has 15 questions comprising

five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The IIEF EF Domain comprises six questions about specific aspects of erectile function, such as whether the patient can obtain erections during sexual activity, penetrate his partner, and maintain his erections after penetrating his partner. The domain also asks the patient to assess his difficulty in achieving erections and his confidence in his ability to achieve and maintain erections. Efficacy was assessed as the change from baseline in the EF Domain score.
SEP Questions 2 and 3 were primary variables in the primary IC351 efficacy studies. Question 2 asked, "Were you able to insert your penis into your partner's vagina?" Question 3 asked, "Did your erection last long enough for you to have successful intercourse?"

The IIEF EF Domain and patient SEP diary scores for Question 2 and Question 3 were the primary efficacy variables. For efficacy analysis, all patients with baseline and post baseline observations on all variables included in the statistical model were included. Questionnaire responses were treated as continuous variables.

IIEF variables (including domains) were analyzed at 12 weeks, utilizing the LOCF convention. The baseline and endpoint scores for IIEF variables are the Visit 2 score and the Visit 5 score, respectively, after application of the LOCF algorithm.

The baseline and endpoint score for each SEP question is the patient's percentage of "yes" responses to that question during the run-in period (that is, the interval between Visit 1 and Visit 2) and the post baseline period, respectively. For any individual sexual encounter, if the patient answered "no" for any SEP question, subsequent questions were analyzed as "no" responses.

Other efficacy variables
For secondary variables, the sponsor used the following:

- SEP Questions 4 and 5 which asked if the patient was satisfied with the hardness of his erection and with his overall sexual experience, respectively. Efficacy was assessed as the change from baseline in the percentage of "yes" responses to the two questions.

- Global Assessment Questions (GAQ)

The GAQ was a secondary variable in the six primary IC351 efficacy studies.

ANCOVA models were used to evaluate change-from-baseline efficacy variables, and the models included terms for baseline value of the efficacy variable, treatment group, pooled site, and the baseline-by-treatment-group interaction. P-values were based on least-squares means from Type III sums of squares; for primary efficacy analyses, they were adjusted for multiplicity.

Medical officers Comments:
The primary and secondary variables used by the sponsor are acceptable for this indication.

2.2.2. Efficacy results

Primary endpoints
The efficacy of IC351 (LY450190) in the treatment of erectile dysfunction (ED) was established in six adequate, well-controlled, multicenter clinical studies which were conducted in Argentina, Australia, Canada, Mexico, Spain, and Taiwan. One of these studies (LVBK) included only patients with diabetes mellitus. The time to onset of the period of responsiveness and the duration of the period of responsiveness were evaluated in studies conducted either wholly or partially in the United States (US). The patient population in Phase 3 included patients with all ED severities (mild, moderate, and severe) and etiologies (organic, mixed, and psychogenic).

Compared to placebo, IC351 significantly improved erectile function and subsequent sexual performance as measured by the IIEF (EF Domain), SEP 2 and SEP 3. The 2.5 mg dose was not successful in all of the 3 primary endpoints. The 5 mg dose provided significant improvement in IIEF and SEP 3 scores (P <.001), but was not statistically significant in SEP 2 (p=.064) in one trial. The 10 mg and 20 mg doses provided statistically and clinically significant improvement in ED in all the end points tested in these trials. The 20 mg dose of IC351 provided some improvement over 10 mg only in the sub group of ED patients with severe disease (pooled data: Studies LVBN, LVCE, LVCO, LVCQ, and LVDJ- see Table 27). However in placebo controlled pivot trials where 10 and 20 mg doses were used against placebo (LVBK, LVDJ, LVCO, the efficacy results for active treatment were similar (Table 28).

Global Assessment Question (GAQ)

Overall, 81% of patients who received 20 mg IC351 reported improved erections by the GAQ. Sixty-seven percent of patients receiving 10 mg IC351 reported improved erections, and 50% of patients receiving 5 mg IC351 reported improved erections. Patients with all degrees of ED severity reported improved erections with IC351 treatment.

Medical officers Comments:

The 5 mg dose showed clinical significance in large number of patients tested in the pivotal trials (n=151). The 10 and 20 mg doses achieved all endpoints of efficacy.

2.2.3. Proposed label indication

The data provided by the sponsor in this NDA are sufficient to support the efficacy claim that "Cialis ™ (20 mg) is indicated in the treatment of male erectile dysfunction." Due to safety concerns, however, the therapeutic index (risk/benefit ratio) does not support its approval at the present time.

2.3. Safety

2.3.1. Exposure to study drug

Clinical studies were conducted in a variety of countries with a diverse population of subjects. More than 950 subjects participated in seven studies in the United States. In over 60 completed and ongoing studies, IC351 has been administered to more than 4000 male subjects.

The primary placebo-controlled Phase 3 trials included 1328 patients with ED and the doses studied in these trials ranged from 2.5 mg to 20 mg IC351. Across all clinical trials, single doses of up to 500 mg IC351 and multiple daily doses up to 100 mg IC351 were administered to healthy subjects and/or patients with ED. A total of at least 500 patients were exposed to the proposed dose of 20 mg IC351 (or an equivalent) for at least one year, and 800 patients have been exposed to 20 mg IC351 (or an equivalent) for at least 6 months.

Table 1 Studies Included in the Integrated Summary of Safety

STUDY GROUP	STUDIES
Primary placebo-controlled integrated database	LVBN, LVCE, LVCQ, LVCO, LVDJ, LVBK
Open-label, long-term safety studies	LVBL, LVBD
Clinical pharmacology studies	> 40 STUDIES
Secondary studies	LVBG, LVBF, LVAC LVBE, LVBI
Secondary market image studies	
Period of responsiveness studies	LVBJ, LVCK, LVDG
Studies with active control	LVCF, LVBO, LVCY
Female sexual dysfunction studies	LVBQ, LVBR
Other ongoing studies	LVDR, LVCR
Semen characteristics studies	LVCD, LVCZ

Medical officers Comments:

Based on the safety data in the present application, the exposure to the 20 mg dose of

Cialis™ is considered adequate to assess its general safety for the indication of treatment of male erectile dysfunction. Some special safety issues remain.

2.3.2. General safety findings

2.3.2.1 Common Treatment Emergent Adverse Events (TEAEs):

- Headache, dyspepsia, back pain, myalgia, rhinitis (nasal congestion), and vasodilatation (flushing) occurred in greater than 2% of the IC351-treated patients and were more frequent than in placebo-treated patients. Headache and dyspepsia showed a higher incidence with the 20 mg dose in 2 pivotal studies; clinical pharmacology studies showed a higher incidence of back pain and myalgia in patients with diminishing renal function.
- The following adverse events occurred in greater than 2% of the IC351-treated patients but were similar or lower in frequency compared with the placebo-treated patients: infection, pain, flu syndrome, dizziness, cough increased, pharyngitis, and surgical procedure.

2.3.2.2 Serious Adverse Events (SAEs):

- In the primary placebo-controlled Phase 3 database, 540 of 949 (56.9%) reported at least one treatment-emergent adverse event compared with 181 of 379 (47.8%) placebo-treated patients. Serious adverse events were reported by 15 patients. In the IC351-treated group, 9 of 949 patients (0.9%) reported at least one serious adverse event compared with 6 of 379 (1.6%) of placebo-treated patients. When adverse events were analyzed for degree of maximum severity in the IC351-treated group, only 7.8% of IC351 treated patients had a severe treatment-emergent adverse event compared with 6.1% of placebo treated patients.
- Overall, 144 patients (10.8%) discontinued from the studies. The most common reason for not completing the studies was personal conflict or other patient decision (37 patients, 2.8%). 27 patients (2.0%) discontinued due to adverse events (5 of 379 patients (1.3%) in the placebo group and 22 of 949 patients (2.3%) in the IC351-treated group.

- The open-label studies LVBL, LVBD and LVDR provide information on the safety and tolerability of IC351 administered long-term. There were 7.3%, 4.4% and 4.2% *serious adverse events* noted in these studies respectively.

- 1034 subjects received at least one dose of IC351 in the 42 completed clinical pharmacology studies. ***Five serious adverse events*** occurred in four subjects. Three of the serious adverse events occurred following placebo administration, and one subject experienced two serious adverse events following IC351. None of the serious adverse events was attributed to administration of the study drug.

2.3.2.3 Patient deaths

As of 28 May 2001, **a total of 7 deaths were reported** from more than 4000 subjects who received IC351. Of these deaths, one was in study LVCY and 6 were in study LVBL. The review of these events showed no direct causal relationship between any of the deaths and IC351. However, one can not unequivocally rule out its association in one study LVCY

2.3.2.4 Patient Discontinuations Due to Adverse Events

In all controlled studies in which IC351 was used as market image formulation and taken at- home as needed, 1.7% of IC351-treated patients and 1.1% of placebo-treated patients discontinued due to adverse events. These differences were not statistically significant. The discontinuation rates due to adverse events in the open-label, long-term safety studies, LVBD, LVBL and LVDR were 4.4% , 5.4 % and 5.7% respectively.

Medical officers Comments:
In the opinion of this reviewer, 5mg or 10 mg should be the starting dose for a vast majority of the these patients based on their ED severity. The patients need this option and flexibility to titrate up the dose if needed and safety permits. These drugs do have a potential for additive hypotensive effect with other vasodilators that could be significant. Some of the common adverse events are explainable while others such as backaches and myalgias are not. They present unknown risk for this drug at present time . These events were seen more frequently with 20mg dose in the patients with compromised renal function.

2.4. Formulation and dosing

CIALIS™ will be available as yellow, almond-shaped, film-coated tablets containing 20 mg of the active ingredient. Following are the chemistry highlights of the drug substance:

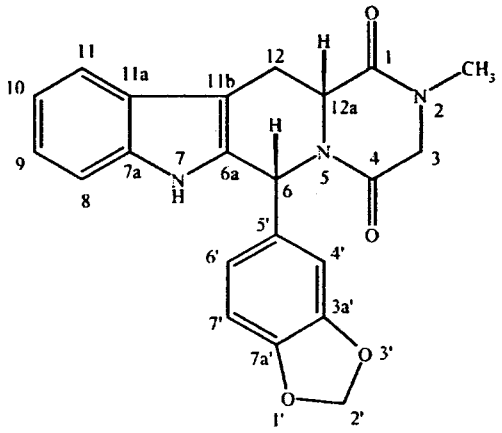
Generic name:	Tadalafil
Chemical Name (CAS):	Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6, 7,12,12a-hexahydro-2-methyl-, (6R,12aR)
Proposed Trade Name:	Cialis
Physical form:	Solid

Empirical formula: $C_{22}H_{19}N_3O_4$

Molecular Weight: 389.41

Inactive ingredients: croscarmellose sodium, hydroxy propyl cellulose, hydroxy propyl methyl cellulose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

Structural Formula:



Dose: 10-20 mg PO Daily

2.5. Special Populations

Geriatric: Of the total number of patients in the primary efficacy and safety studies of tadalafil, 27% were age 65 and over. Healthy elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. Also noted was the increased severity in the adverse events in some patients. The effect of age should not warrant a dose adjustment in otherwise healthy elderly men. However, some patients will require lower doses.

Pediatric : Tadalafil has not been evaluated in individuals less than 18 years old.

Hepatic Insufficiency: Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) was comparable to exposure in healthy subjects. No dose adjustment is required in these patients (see study **LVAK**).

Renal Insufficiency: In subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal impairment, tadalafil exposure

(AUC) was higher than in healthy subjects as shown in a clinical pharmacology study. This group of patients may need a lower starting dose (5 mg). Tadalafil has not been studied in subjects with severe renal impairment (creatinine clearance ≤30 mL/min). The drug should be contraindicated in elderly males with severe renal impairment (creatinine clearance ≤30 mL/min).

Patients with Diabetes: Tadalafil exposure (AUC) in patients with diabetes was approximately 19% lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

Pregnancy, Nursing Mothers and Pediatric Use: Cialis™ is **not** indicated for use in newborns, children or women.

Clinical Review

3. Introduction and background

3.1 DRUG PRODUCT

Drug established and proposed tradename, drug class, proposed indication(s), dose, regimen-

Drug product:	Cialis™
Drug substance:	Tadalafil
Dose:	20 mg
Dosing Regimen:	Administered once daily
Route of administration:	Oral
Pharmacological class:	Phosphodiesterase -V inhibitor
Indication:	Treatment of male erectile dysfunction

3.2. Overview of disease and treatment options

3.2.1 Male Erectile Dysfunction and medical therapy

Penile erection is mediated by neural stimuli that ultimately cause vasodilation of the arteries and sinusoidal spaces of the corpus cavernosum. As the arteries dilate, blood flow to the cavernosum increases. As the smooth muscle of the cavernosal sinusoidal spaces relaxes, draining veins are occluded and the cavernosum becomes engorged with blood, leading to an erection.

Because erectile tissues are vascular, many vasoactive compounds have been investigated for their therapeutic potential in ED. The first widely available treatments were compounds that were directly injected into the corpus cavernosum, either alone or in combination. These compounds included papaverine, prostaglandin E1 (PGE1), and phentolamine. Alprostadil (PGE1) delivered by intraurethral deposition has also become available for the treatment of ED. However, most patients prefer oral therapies to any other route of administration.

Nitric oxide (NO) is believed to play a central role in vasodilation of erectile tissues because it relaxes smooth muscle by increasing guanylyl cyclase activity, which in turn raises intracellular cyclic guanosine monophosphate (cGMP) concentrations. PDEs are a diverse group of enzymes that have a variety of tissue distributions and functions; however, they ultimately act to lower intracellular cyclic nucleotide levels. There are at least eleven different currently known PDE classes, many with subtypes identified by structure and function. PDE5 inhibition potentiates the relaxant effects of NO by inhibiting hydrolysis of cGMP, thereby increasing cGMP levels in the cell. This eventually lowers the intracellular Calcium and thereby relaxes the smooth muscle allowing the erection to take place.

The proposed 20 mg dose has a mean C_{max} of 378 ng/mL and an AUC of 8066 mg·h/L. The median T_{max} is 2 hours. The mean $t_{½}$ is 17.5 hours.

3.2.2. Important issues with pharmacologically related agents

General safety

The PDE V inhibitors have a vasodilatory action. PDEs are a ubiquitous group of enzymes. In the placebo-controlled, market image formulation, eleven "at home" studies conducted by the sponsor (LVCK, LVCY, LVBO, LVCF, LVCE, LVBN, LVCO, LVCQ, LVBK, LVDJ, LVDG), headache (11%), dyspepsia (7%), back pain (4%), myalgia (4%), nasal congestion (4%), and flushing (4%) were the most frequent events in the IC351-treated group. The association of these adverse events with IC351 and of PDE5 inhibitors is plausible. The pathogenesis of back pain and myalgia is currently not understood. These events present unknown safety risk and may be related to exposure to the drug or its metabolite, methyl catechol glucuronide.

Cardiovascular Safety

Sexual activity itself, by virtue of the demands it places on the cardiovascular system, is associated with a risk of cardiovascular adverse events including myocardial infarction. This is compounded by the fact that PDE 5 inhibitors do have some vasodilatory effect, although small; hence, combined use with nitrates is generally contraindicated. Concomitant use of other vasodilatory agents should be done with caution.

Human Sperm Characteristics and Spermatogenesis

Two studies conducted by the sponsor were randomized, double-blind placebo-controlled 6-month studies to evaluate the effects of 10 mg (LVCD) and 20 mg IC351 (LVCZ) given daily on semen characteristics in healthy subjects and subjects with mild erectile dysfunction. These studies did not show clinically significant effects on commonly accepted semen parameters.

Visual Safety

Phosphodiesterase inhibitors have the potential to affect visual function. The mechanism is believed to involve the inhibition of PDE6, an enzyme found in the retina and thought to be responsible for photo transduction. The sponsor contends that the selectivity of IC351 for PDE5 is approximately 700 times that for PDE6 and the visual abnormalities were clinically insignificant in the studies with IC 351. However, the FDA ophthalmologist reviewed this data and found many deficiencies in the submitted studies. He felt that the incidence of visual abnormalities seen with this product was the same as another drug in its class and that this fact should be reflected in the label.

3.3. Important milestones in product development

The first oral phosphodiesterase V inhibitor (Sildenafil) was approved by FDA in 1998.

On 6 November 1997, ICOS Corporation submitted an Investigational New Drug (IND) application (IND 54,553) for IC351 to the Division of Reproductive and Urologic Drug Products (DRUDP) for the treatment of erectile dysfunction. The IND was received at FDA on 10 November 1997. On 9 December 1997, IND 54,553 was placed on clinical hold due to preclinical safety concerns. Information needed to resolve the clinical hold was conveyed in a letter from FDA dated 16 December 1997. The following information was requested:

· Reports from the [redacted] 6-month rat and dog toxicity studies

· A 6-month oral toxicology study in monkeys was recommended to help determine if vasculitis is species-specific in dogs.

· Identification of biomarkers to monitor for vasculitis in men

· Enzyme kinetic data for phosphodiesterase (PDE) isozymes

· Multiple-dose pharmacokinetic data for the target population

· Identification of the metabolite profile in men, including determination of whether major metabolites are biologically active.

In correspondence dated 5 February 1998, FDA sent comments on a proposed Phase 2 clinical protocol, which did not involve clinical hold issues. The correspondence also included some chemistry questions.

On 24 April 1998, additional information was submitted to FDA in response to the clinical hold. On 15 May 1998, draft interim pharmacokinetics report (LVBH [DSD02]) was submitted to FDA in response to the clinical hold. Agreement was reached in a face-to-face meeting between ICOS and FDA personnel on 26 May 1998 to proceed with human clinical trials prior to additional preclinical data submitted to the IND.

On 26 June 1998, a protocol synopsis for study (LVBF [DSD06]) was submitted to FDA for comment. Final protocol LVBF was submitted to FDA on 3 July 1998.

In correspondence from FDA dated 20 July 1998, additional pharmacology review comments were conveyed. These comments were as follows:

Safety pharmacology studies were recommended to assess the effects of IC351 on gastrointestinal motility and gastric acid secretions

Request to repeat the mouse lymphoma mammalian cell mutation assay using higher dose levels.

Results of in-vivo geno toxicity assay need to be provided prior to Phase 2 clinical trials.

In a teleconference with FDA on 27 July 1998, ICOS agreed to amend protocol LVBF to monitor patients' erythrocyte sedimentation rate (ESR ; Surrogate Bioindicator for vasculitis). The amended protocol LVBF was submitted to FDA on 27 July 1998. The clinical hold was lifted on 29 July 1998, and it was requested that the study report for LVBF be submitted prior to proceeding with additional U.S. clinical trials.

The final study report for LVBF was submitted to the IND on 9 March 1999, and on 26 April 1999, Lilly ICOS requested the review of two protocols, LVBM and LVBK.

On 10 May 1999, Lilly ICOS submitted a request for a Carcinogenicity Assessment Committee (CAC) review for approval of the proposed doses for the oncogenicity studies in rats and mice.

In a teleconference between DRUDP and Lilly ICOS on 9 June 1999, the following was agreed :

20 mg IC351 is an acceptable dose from a safety perspective

· Primary endpoints should be the International Index of Erectile Function (IIEF) Erectile Function Domain and Sexual Encounter Profile (SEP) patient diary Question 2 and Question 3

· Exclusion criteria for cardiac arrhythmias should be revised so patients with benign arrhythmias can be included in trials

· Active treatment duration was increased to 12 weeks

· Specific analysis of QTc interval was not planned, but a consult with Division of Cardio-Renal will occur when a protocol is submitted

· Any secondary endpoints need to be adjusted for multiple comparisons and need to be derived from validated instruments to be considered to support the label

· Ophthalmology studies will be consulted to Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

· Use of short-acting nitrates by patients in trials will be considered pending review of the clinical nitrate/drug interaction study data.

The dose selections for the 2-year rat and mouse carcinogenicity studies were acceptable, as conveyed in the CAC meeting minutes dated 15 June 1999. In addition, circumstances were outlined for additional histopathology in the studies. In a teleconference on 23 June 1999, Dr. El Hage of FDA agreed that a gastric acid secretion study is not needed.

An IND animal safety report was submitted to FDA on 21 July 1999 that described compound-related testicular alterations in the 6-month chronic toxicity study in beagle dogs.

On 30 July 1999, a briefing document was submitted for a requested meeting with FDA.

In Chemistry, Manufacturing and Control (CM&C) meeting minutes dated 6 August 1999 the following were agreed:

· The proposed starting materials are acceptable;

· The New Drug Application (NDA) should include : justification for variances from International Conference on Harmonization (ICH) guidelines in the stability program; representative impurity profile chromatograms for the active pharmaceutical ingredient (API); justification for variances from ICH guidelines in residual solvent limits; the data, a database summary, and justification for the use of in the dissolution test; and chiral inversion data;

· A specification for methylamine is not needed provided Lilly ICOS can provide proof that the methylamine is totally eliminated during the manufacturing process;

· Particle size and surface area need to be included in the specifications if they are important to the process control;

· A single-point specification at the time points proposed for the dissolution test are acceptable;

· Matrixing across strengths packaged in bottles is acceptable in principal. It was agreed that Lilly ICOS would choose a matrix design for drug product stability and will submit the data for statistical review prior to NDA submission.

At the meeting with FDA on 30 August 1999, the following were agreed:

· Phase 3 trial comments – the proposed approach regarding dose selection is acceptable; the SEP is not considered validated but the revisions are acceptable; and patients on short-acting nitrates will be excluded

· One-year exposure for safety needs to be at exposures equivalent or above the marketed doses

· The proposal for financial disclosure information is acceptable

· Waiver for pediatric studies should be requested in NDA. In addition, Lilly ICOS agreed to propose a safety study to address the seminiferous tubule damage issue and to submit the full protocol of study LVBY (nitrates) for review.

Visual study protocol LVAN was discussed in a teleconference between Lilly ICOS and FDA on 8 September 1999.

On 4 October 1999, Lilly ICOS submitted a protocol outline for the sperm assessment study LVCD.

On 29 October 1999, FDA indicated that a 1-year dog toxicity study is needed to support safe clinical dosing beyond a 6-month duration. This was in response to the submission of the second 6-month dog toxicity study on 12 August 1999.

Draft protocol LVCC (visual study) was submitted for review on 3 November 1999.

Visual study protocol LVAN was discussed in a teleconference between Lilly ICOS and FDA on 8 September 1999.

On 4 October 1999, Lilly ICOS submitted a protocol outline for the sperm assessment study LVCD.

On 29 October 1999, FDA indicated that a 1-year dog toxicity study is needed to support safe clinical dosing beyond a 6-month duration. This was in response to the submission of the second 6-month dog toxicity study on 12 August 1999.

Draft protocol LVCC (visual study) was submitted for review on 3 November 1999.

On 5 November 1999, FDA provided interim guidance on the sperm assessment safety trial. Specifically, FDA indicated that semen assessment should be performed at Week 13 as well as Week 26, a Data Monitoring Board (DMB) should review these results to determine if Phase 3 trials can be initiated, and criteria to initiate Phase 3 trials should be provided to DRUDP in advance of their initiation. Additionally, FDA requested that patients with mild ED, with mild-moderate ED, and normal (no ED) subjects at least 45 years old should be included in these trials. FDA also indicated that the proposed endpoint using a mean analysis of sperm count is not appropriate, so a teleconference was scheduled for 2 December 1999 to reach agreement on the endpoint for this study.

An IND animal safety report was submitted to FDA on 24 November 1999 stating that neutropenia, thrombocytopenia, and/or decrease in hematocrit was observed in one mid-dose and one high-dose female in the 12-month dog study.

A teleconference to discuss the sperm assessment study was held on 2 December 1999. The endpoint agreed upon was proportion of subjects with reduction in sperm concentration of greater than or equal to 50% from baseline. Also, monthly complete blood count (CBC) monitoring was recommended based on the 24 November 1999 safety report, and DRUDP agreed to discuss the clinical relevance of results. Finally, FDA indicated that Phase 3 trials could not be initiated until after the DMB assessment of the Week 13 samples, although an adverse result in the trial will not necessarily signal an end to clinical development of IC351. Sperm assessment protocol LVCD was submitted to FDA on 17 December 1999.

Comments from FDA on visual study protocol LVCC were received by Lilly on 4 January 2000.

On 4 February 2000, Lilly ICOS submitted a request for review of Cialis™ as the proposed trademark for IC351.

In correspondence dated 17 February 2000 regarding sperm assessment protocol LVCD, the FDA requested information regarding the exact statistical methodology to be used to answer the specific question asked in this study, and the FDA accepted the proposed independent DMB guidelines for the interim safety data assessment. The statistical methodology to be used in protocol LVCD was submitted to FDA on 6 March 2000.

On 15 March 2000, Lilly ICOS submitted additional information, requested by DRUDP, needed to complete preliminary review of the Cialis™ trademark.

Amended protocol LVCD was submitted to FDA on 3 April 2000.

A briefing document describing the proposed nitrate interaction package was submitted to FDA on 9 May 2000. On 16 June 2000 in a teleconference with the FDA Project Manager, a proposal was made to expand the requested nitrate interaction meeting to include a discussion of the clinical plan for the 20-mg IC351 dose. On 30 June 2000 an additional briefing document for the 3 August 2000 meeting was submitted that supplemented the 9 May 2000 briefing document by summarizing the proposed changes to the clinical registration plan for 20 mg IC351.

An IND animal safety report was submitted to FDA on 25 July 2000 that described compound-related testicular alterations in the 1-year chronic toxicity study in beagle dogs.

The following comments and agreements resulted from the 3 August 2000 meeting between Lilly ICOS and FDA:

· Division of Cardio-renal recommended that a) nitrate safety studies include higher IC351 doses (e.g., 80 mg) to provide information on adequate margin of safety, and b) a positive control group be used in nitrate safety studies

· The proposed analysis plan for nitrate interaction studies is acceptable

· If pharmacology studies had demonstrated no interaction between IC351 and nitrates, use of nitrates in Phase 3 could be allowed

· The 3-month assessment showing non-inferiority to placebo in sperm assessment study (LVCD) 10 mg IC351 is acceptable to support Phase 3 studies at 20 mg IC351

· There were concerns regarding sample size for the addition of a 20-mg IC351 treatment group to the existing study LVCD and regarding pooling placebo groups

· Semen assessment is not needed in open-label study LVBL since results will be obtained using 20 mg IC351 in LVCD using daily dosing

· Lilly ICOS stated that exposures at 6 months and 1 year for 20 mg IC351 will meet ICH guidelines

· Drug-drug interaction studies at 20 mg IC351 using a CYP 3A4 substrate are acceptable; adequacy of studies using 10 mg IC351 with CYP 2C9 and CYP 1A2 will be a review issue

· Extrapolation of pharmacokinetic data from studies conducted with 10 mg to 20 mg IC351 will also be a review (labeling) issue

· Results of pharmacodynamic interaction studies with the 10-mg IC351 dose may not be extrapolated to the 20-mg IC351 dose.

· Lilly ICOS agreed to provide a fully revised version of protocol LVCD to assess 20-mg IC351 sperm effects.

In a teleconference on 11 August 2000, FDA indicated that the proposed analysis plan to add a 20 mg IC351 treatment group to sperm assessment study LVCD and to pool the control group is not acceptable. DRUDP did agree with a reduction in the semen volume criteria to 1.5 mL for that study. Lilly ICOS agreed to provide a protocol for a 20-

mg IC351 sperm assessment study. On 8 September 2000, Lilly ICOS submitted 20-mg IC351 sperm assessment protocol LVCZ.

On 29 September 2000, Lilly ICOS sent FDA a DMB report for study LVCD stating that 10 mg IC351 was similar to placebo with respect to sperm effects (3-month results).

On 13 October 2000, Lilly ICOS submitted to FDA a briefing document for a pre-NDA CM&C meeting.

In a telephone call on 23 October 2000, FDA Project Manager indicated that preliminary review by the Office of Post marketing Drug Risk Assessment (OPDRA) of the trademark Cialis resulted in OPDRA recommending against the use of Cialis as a trademark.

DRUDP, however, had not made a preliminary recommendation for or against the name Cialis at that time.

The following comment and agreements resulted from the 14 November 2000 pre-NDA CM&C meeting:

· The plan to include [redacted] in drug substance packaging was acceptable

· The plan by Lilly ICOS to utilize four primary stability batches to satisfy the batch record requirement was accepted

· The proposal by Lilly ICOS to submit the NDA with 6 months of primary stability data for the 20-mg IC351 tablet and provide 12-month data during the review period was accepted.

On 13 December 2000, Lilly ICOS submitted a request to DRUDP for additional information on the OPDRA review of the trademark Cialis. On 20 December 2000, Lilly ICOS submitted a request for a pre-NDA meeting.

The following transpired at the pre-NDA meeting on 21 February 2001:

· The proposed formats and plans (proposed table of contents, Phase 3 study reports, representative selection of proposed tables and statistical analysis plan) are acceptable for the Phase 3 study reports

· A 3-month analysis report for study LVCQ is adequate to demonstrate efficacy; the integrity of the 6-month data is unknown due to the unblinding at 3 months, therefore the applicability of the 6-month data will be a review issue; an "alpha spend" will not apply. If the final 6-month study report is submitted at or before the 4-month safety update, it will not constitute a major amendment

· The proposed statistical analysis plan for the Integrated Summary of Effectiveness (ISE) is acceptable. FDA requested that conclusions on the explored data in the final dose response decision analysis be submitted in the NDA including dose response information, corrected analysis, and analysis leading to the final recommended dose. FDA requested that the tables that present Last Observation Carried Forward (LOCF) data should include the observed values, presented in a parallel analysis; if study centers are aggregated, a column should be included that identifies the study center in the data set. Also, given that the Phase 3 studies are conducted outside the US, FDA requested that Lilly ICOS provide in the ISE comments on interpretation of cross cultural differences, validation of the efficacy measures, and how data may be applied to the US population.

· The submission of the 6-month study results from study LVCZ will not be a major amendment if submitted at or before the 4-month safety update

· It is acceptable to use exposure data for the ———————— of higher doses in support of meeting ICH exposure requirements for the proposed dose of the market image formulation; it could be a filing issue if ICH exposure requirements are not met at the time of submission

· The proposed statistical analysis plan for the Integrated Summary of Safety (ISS) is acceptable; the Division requests that a special safety section be provided in the ISS to include specific adverse events particularly the incidence and severity of back pain, eye disorders, effect on blood pressure, and cardiovascular and cerebrovascular adverse events; duration of adverse events as it relates to duration of exposure should be included in the safety analysis; sponsor should discuss and present benefit/risk ratio in the NDA

· The number and types of studies as proposed appears to be acceptable to support filing of the NDA

· It is acceptable to provide references in electronic format only

· The plans for the proposed electronic format is acceptable, the guidance document for industry regarding electronic submissions should be followed.

· The approach to financial disclosure reporting information is acceptable. FDA requested that Lilly ICOS provide a table for each study listing the investigators, status of disclosure, and number of patients, as well as a description of the "due diligence" used to obtain information.

· The rationale for a pediatric waiver appears to be acceptable, final determination will be made upon receipt of the waiver request.

· The Clinical Pharmacology Biopharmaceutics Division requested that in vitro interaction studies which provide isoenzyme information 2C19 be included in the submission.

· [redacted] will be a review issue; Lilly ICOS may request a teleconference to discuss this further.

On 26 March 2001, NDA and User Fee ID numbers were assigned to Lilly ICOS for this submission.

On 4 April 2001, Lilly ICOS submitted additional information to address specific concerns raised by OPDRA in their review of the trademark Cialis™. This information included an analysis of the name pairs versus Cialis™Aralen™ and Cialis™versus Claritin™, along with additional information regarding an independent analysis of the name Cialis designed to assess the possibility of name confusion in written prescriptions.

On 5 April 2001, Lilly ICOS submitted a request for a teleconference to discuss the [redacted] regarding the [redacted] of [redacted] per Dr. Mark Hirsch's suggestion at the 21 February 2001 pre-NDA meeting. On 3 May 2001, DRUDP sent correspondence indicating that this request for a teleconference was denied, and that the issues would be considered with the NDA review.

On 18 April 2001, Lilly ICOS submitted an information amendment to IND 54,553 to update DRUDP on four clinical trial deaths that occurred since the one death reported in

the previous IND annual report (10 August 2000). None of the deaths were assessed by investigators or sponsor to be related to study drug or protocol procedures.

3.4. Other relevant information

Cialis™ is not marketed in any international market. No other research- related information on Cialis™, other than that submitted, is available.

4. Clinically relevant findings from chemistry, animal pharmacology and toxicology, microbiology, biopharmaceutics, statistics and/or other consultant reviews

4.1. Toxicology review

According the primary reviewer (Dr.Y. Shin), there is a reason to believe that IC 351 is associated with vasculitis in the beagle dogs and they believe that the label should reflect this. Overall they conclude this product is approvable.

4.2. Clinical pharmacology and biopharmaceutics review

According the primary reviewer (Dr.S.Roy) the submisssion is acceptable. There are biopharmaceutical findings that Indicate a recommendation for 10mg dose along with the 20 mg Cialis™ for the proposed indication male erectile dysfunction. There is also a concern about Drug – Nitrate interaction. There are concerns regarding increased exposure levels of IC 351 (5mg) in patients with mild and moderately impaired renal function. Additionally they feel that there may be an association of adverse events such as back pain and myalgia and the prolonged t ½ (55 hours) of methyl catechol glucuronide in these patients.

4.3. Chemistry review

According the primary chemistry reviewer (Dr. R. Agarwal), there are some chemistry issues under discussion with the sponsor.

5. Human pharmacokinetics and pharmacodynamics

5.1. Pharmacokinetics

Clinical pharmacology studies have shown that IC351 is rapidly absorbed, with the recommended 20 mg dose reaching a mean Cmax of 378 ng/mL and an AUC(0-24) of 8066 µg*h/L. The mean t1/2 is 17.5 hours.

5.1.1. Absorption

IC351 is rapidly absorbed after oral administration, with Cmax in plasma occurring at a median tmax of 2 hours . The extent of absorption from an oral solution is at least 36% of the dose (CSR LVAA). The rate and extent of absorption from the 20 mg tablet are not influenced by food (CSR LVDQ).

5.1.2. Distribution

According to the sponsor , IC 351 is distributed into tissues, as indicated by an apparent volume of distribution (Vz/F) of 62.6 L (Integrated Statistical Analysis Rpt). Over the therapeutic concentration range, 94% of IC351 in plasma is bound to proteins, principally a1-acid glycoprotein and albumin. Protein binding is not affected by renal impairment and is independent of IC351 and metabolite concentrations. Measurement of radioactivity in samples collected from healthy subjects approximately 5 hours after dosing indicates that <0.0005% of the total dose of IC351 is distributed to semen .

5.1.3. Metabolism and Excretion

According to the sponsor ; IC351 is cleared extensively by oxidative metabolism. Metabolism of IC351 to the catechol metabolite (IC711) is principally mediated by CYP3A4, as indicated by in vitro data . The catechol (IC711) undergoes extensive methylation and glucuronidation to form the methylcatechol (IC710) and the methylcatechol glucuronide conjugate (LY559171), respectively. The methylcatechol glucuronide is the major metabolite in human plasma and urine. The term "Total IC710" denotes the concentration of the methyl catechol measured after hydrolysis of plasma with β -glucuronidase; this accounts for both conjugated and unconjugated forms of the methylcatechol. During once-daily dosing, systemic exposure to Total IC710 at steady-state is approximately 30% higher than for IC351. The majority of Total IC710 is the methyl catechol glucuronide, which is not selective for PDE5 and according to the sponsor, is at least 13,000-fold less potent for PDE5 than IC351. However, mild and moderate hepatic impairment did not compromise metabolic clearance of tadalafil and systemic exposure (AUC) to tadalafil was similar across subject groups.

Mass balance studies suggest that tadalafil is extensively metabolized and 61% is excreted in the feces and 36% in urine. Renal impairment had a greater effect on the disposition of methyl catechol glucuronide than on tadalafil, as expected for a renally-cleared metabolite. Systemic exposure was 2-fold higher in subjects with mild and moderate renal impairment. Since this metabolite is primarily cleared by the renal route, in moderate renal impairment the exposure to methyl catechol glucuronide was 3.6-fold higher (t ½ = 55hours) and was associated with higher incidence of musculo-skeletal adverse events such as myalgia and back pain. Due to the increased incidence of adverse events in moderately impaired subjects, no subjects with severe renal impairment received tadalafil.

5.1.4 Elimination:

Following administration of approximately 100 mCi of [14C]-IC351 (approximately100 mg) to healthy subjects as a solution in polyethylene glycol 400 (PEG 400), approximately 61% of the radiolabel dose was excreted in feces and approximately 36% was recovered in urine . Less than 0.3% of the dose appears in urine as unchanged IC351, indicating negligible renal clearance of theparent drug (CSR LVBS). The kidney, however, is an important route of excretion for the catechol glucuronide and methylcatechol glucuronide metabolites.

Biliary secretion is likely to be an important route of elimination of IC351 and/or its metabolites. In healthy subjects, apparent oral plasma clearance (CL/F) of IC351 is 2.48 L/h (5thto 95thpercentiles of 1.35 to 4.35 L/h), indicating that IC351 has a low hepatic extraction ratio. The corresponding mean t1/2 value is 17.5 hours (5thto 95th percentiles of 11.5 to 29.6 hours)(Integrated Statistical Analysis Rpt). The t1/2 for Total IC710 in plasma is essentially similar to that for the parent drug, indicating that elimination of the metabolites may be formation-rate limited. Pharmacokinetics of IC351 are linear with respect to time and dose over a 2.5 mg to 20 mg range. Systemic exposure (AUC) increases proportionately with dose up to 20 mg (CSR LVBX). During once-daily 20 mg dosing, steady-state plasma concentrations are attained within approximately 5 days and the degree of drug accumulation is 1.6 - fold. The intra-subject variability estimated for AUC and Cmax were 13.3% and 15.8%, respectively . The major difference in the concentration-time profiles was in terms of the terminal elimination half-life, the mean half-life in the elderly group was approximately 5 hours longer than that of the young group. The adverse events incidence increases with renal impairment (Table 2)

Table 2: Treatment-emergent adverse events following administration of 10 mg tadalafil vs renal function:

Group	Subjects with adverse events (%)
Healthy subjects	1/8 (12.5)
Mild renal impairment	1/5 (20)
Moderate renal impairment	5/6 (83.3)

Medical Officers comments:

These findings do indicate a potential for higher adverse events, particularly back pain and myalgia in patients with compromised renal function. The mechanism of these events is yet unknown and pose an unknown safety risk.

This reviewer believes that IC351 20mg should be contraindicated in patients with severe renal failure. The patients with mild to moderate renal failure should be started on low dose of 5mg and titrated up to 10mg with warning of adverse events

5.2. Pharmacodynamics and Drug –Drug Interactions

The potential for IC351 to augment the hypotensive effects of antihypertensive compounds was investigated in a number of studies. The sponsor conducted some studies using only a 10 mg dose, while in some studies a dose of 20mg was used.

There was no evidence of a clinically significant pharmacodynamic interaction of single 10 mg doses of IC351 with a beta-blocker (LVAW), a thiazide diuretic (LVAX), or an angiotensin-converting enzyme (ACE) inhibitor (LVBC) in hypertensive subjects. Studies in healthy subjects did not reveal clinically significant evidence of a pharmacodynamic interaction between 10 and 20 mg IC351 and either a calcium antagonist (LVAV, LVDP) or an alpha-blocker (LVAY).

For hypertensive subjects taking angiotensin II receptor antagonists as monotherapy or as part of a multi-therapy regimen, there was a statistically significant fall in ambulatory systolic blood pressure following 20 mg IC351 (LVDS). Ambulatory diastolic blood pressure and heart rate were similar between treatments and there were no apparent differences in the tolerability profile.

There was a small increase in heart rate when theophylline was given with 10 mg IC351 compared to theophylline alone (LVAP). The significance of this is unclear and since 20 mg is the dose sought it should have been the dose tested. There were no clinically significant changes in blood pressure.

There was no evidence that co-administration of 10 mg IC351 affected the prolongation of bleeding time with aspirin (LVBV) or altered the effect of warfarin on prothrombin time (LVAQ).

Medical Officers Comments:
It is notable that 10mg doses were used for interactions with aspirin, warfarin, B blockers , theophylline, thiazides , nitrates and ACE inhibitors. Some of these agents have vasodilatory properties in their own right and if the sponsor is seeking a dose of 20 mg , it is required that the sponsor study the interaction with the dose sought to determine the additional hemodynamic changes.

The data with 10mg may not be extrapolated to 20mg dose of IC 351.

5.2.1 Nitrate interaction studies
were conducted in healthy subjects (LVAB, LVCM) and in subjects with chronic stable angina (LVBY). At dose levels of 5 and 10 mg, IC351 appeared to potentiate the hypotensive effect of organic nitrate up to 24 hours after dosing, particularly in subjects with chronic stable angina. Although there appeared to be a small residual effect after this time, this may reflect the long ½ life of tadalfil. Potentiation of the hypotensive effect was more pronounced for short-acting nitrates than for a chronically administered long-acting nitrate therapy (LVBY).

5.2.1.1 Short-acting Nitrates

A phase 1 single-center study was conducted to study pharmacodynamic interaction of tadalafil with short-acting nitrates.

1) Part A of this study was a double-blind, randomized, placebo-controlled, two-way crossover comparing blood pressure and heart rate responses to nitroglycerin after daily dosing of tadalafil and placebo for 7 days each in healthy male subjects. Nitrate administration consisted of a graded dose infusion of intravenous nitroglycerin for approximately 30 minutes on one occasion and a single dose of sublingual nitroglycerin (0.4 mg) on the other.
2) Part B was an open-label, randomized, two-way crossover comparing blood pressure and heart rate responses to nitroglycerin after a single dose of 10 mg tadalafil or 50 mg sildenafil in healthy male subjects. Intravenous nitroglycerin was administered at the time of expected maximum plasma concentration of each drug (1 hour after sildenafil and 3 hours after tadalafil). No sublingual nitroglycerin was administered in Part B.

The mean plasma tadalafil concentration at 3.5 hours in Part A was 162.3 µg/L on the day of intravenous nitroglycerin administration and 162.0 µg/L on the day of sublingual nitroglycerin administration. In Part B, the mean plasma tadalafil concentration at 3.5 hours after dosing was 105.9 µg/L.

- The mean maximal nitroglycerin-induced decrease in SBP was 18 mm Hg for placebo and 20 mm Hg for 10 mg tadalafil.
- The absolute nadir SBP value was lower for 10 mg tadalfil (7 mm Hg, p= 0.013) than placebo.
- The mean maximal compensatory increase in heart rate was 20 bpm for10 mg tadalafil compared with 19 bpm for placebo.
- Nitroglycerin sensitivity was increased during multiple daily doses of tadalafil. In addition, no difference was observed between multiple dose tadalafil and Sildenafil.
- Headache, dyspepsia, and back pain were the most common treatment-related adverse events in this study.

A survival analysis was conducted that compared the maximally tolerated nitroglycerin infusion rate during each of the four treatment arms: multiple dose placebo, single dose 10 mg tadalafil, multiple dose 10 mg tadalafil, and multiple dose 50mg sildenafil. The distribution of subjects to doses at which they reached the pharmacodynamic endpoint, by treatment was determined. The percentages of subjects who were able to tolerate the highest dose of nitroglycerin were 36%, 27%, 10% and 9% multiple dose placebo, single dose 10 mg tadalafil, multiple dose 10 mg tadalafil, and multiple dose 50 mg sildenafil, respectively.

Table 3:Survival analysis and relative risk NITRATES+ (IC351/Sidenafil)

Treatment Comparison		Survival (with frailty)		
Treatment 1	Treatment 2	Relative Risk (Trt 2 vs Trt 1) RR	95%CI	p-value
Placebo MD	IC351 10mg SD	1.66	(0.79, 3.46)	0.178
Placebo MD	IC351 10mg MD	1.93	(0.92, 4.06)	0.084
Placebo MD	Sildenafil 50mg SD	2.66	(1.31, 5.41)	0.007
IC351 10mg SD	IC351 10mg MD	1.16	(0.57, 2.37)	0.679
IC351 10mg SD	Sildenafil 50mg SD	1.61	(0.82, 3.15)	0.166
IC351 10mg MD	Sildenafil 50mg SD	1.38	(0.70, 2.74)	0.353

Medical Officer's Comments:

- Nitroglycerine , a potent vasodilator , alone, produced a hypotensive effect of 12-18 mm/hg. The additional hypotensive effect of IV nitroglycerine **and IC351**, in one study, (at the plasma concentrations of 105.9 µg/L- 162.3 µg/L of tadalafil) was small (2-5mm) , when compared to placebo and followed upto 30 minutes. In another study with sublingual NTG and tadalafil the patients were followed upto 6 hours with similar findings. This study is useful in hospital setting but does not answer the question ; when is it safe(and how much) to give Nitrates in patients who are on IC 351?
- Tadalafil has a half life of 17.5 hours and therefore can stay in the system for 4-5 days and longer.
- The additive effect of nitrates in presence of IC 351 (particularly when proposed 20mg dose is used) could be significant and with the current available data, use of IC 351 should be contraindicated in patients currently on Nitrates. The sponsors were advised by cardiorenal division to use doses of up to 80 mg of IC 351 in nitrate interaction studies for a good margin of safety .
- The occurance of angina in patients taking IC 351 does present an acute management problem in the real world and will require an additional risk management plan. This can be accomplished by doing a study outlining the qualitative and quantitative effects of IC351 and Nitrate (preferably including doses up to 80mg) for the entire duration of IC 351 exposure.

5.2.2 Alcohol Interaction Studies:

1) A Phase I, subject and investigator blind, placebo-controlled, randomized, four-period cross-over study (Study LVAE) was conducted in 16 healthy male subjects to investigate the potential pharmacodynamic interaction between alcohol and tadalafil. In addition, the effect of tadalafil on the pharmacokinetics of alcohol were determined. A dose level of 0.7 g/kg of alcohol was used in this study in order to produce effects on cognitive function and voluntary co-ordination that are typical of alcohol.
This study was notable for the following:

- Values for Cmax ranged from ——— mg/dL and ——— mg/dL following administration of alcohol in the presence and absence of tadalafil, respectively. These levels are close to 80 mg/dL, the legal intoxication level in the UK and several states in the USA.
- Following co-administration of tadalafil with alcohol, there were *trends* for impairment of some parameters (postural stability and word recognition) compared to the administration of alcohol with tadalafil placebo.
- The decrease in mean standing diastolic blood pressure was larger (–12 mmHg at 4 hr) for the tadalafil and alcohol combination compared to tadalafil with alcohol placebo, alcohol with tadalafil placebo, and tadalafil placebo and alcohol placebo.

Some notable patients are shown in Table 4

Table 4:Clinically significant events IC 351(10mg) + alcohol

Treatment	Blood Pressure Parameter	Subject	Time after alcohol dose (h)	Baseline (mmHg)	Blood Pressure (mmHg)	Decrease from Baseline (mmHg)
IC351 & alcohol	Supine diastolic	8	2	74	45	-29
			4	74	47	-27
			6	74	51	-23
		9	2	56	37	-19
	Standing diastolic	8	4	79	55	-24
	Standing systolic	13	6	114	81	-33

2) Another randomized, placebo-controlled, subject and Investigator-blind, two-period