DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED BY FACSIMILE**

Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly ICOS LLC
c/o Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

**RE:** **NDA** [redacted]
IC351
MACMIS ID#10598

Dear Dr. Brophy:

This letter objects to Lilly ICOS LLC's (Lilly ICOS) dissemination of violative promotional materials for its investigational product, IC351. As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of websites for IC351 that are false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, Lilly ICOS is promoting its investigational new drug, IC351, as being safe and effective for the uses under investigation (i.e., erectile dysfunction).

Section 21 CFR 312.7 states, among other things, that an investigational new drug may not be promoted as being safe or effective for the uses under investigation. However, the following websites[1,2,3] include claims describing the safety or effectiveness of IC351, an investigational treatment for erectile dysfunction. For example, you present claims including, but not limited to, "A therapy that allows a man with ED to engage in intercourse within a 24-hour window permits the couple to regain spontaneity in their sexual relationship," "These findings suggest that dosing for Cialis should be simple and uncomplicated...," "Following sexual stimuli, Cialis relaxes blood vessels by inhibiting the enzyme PDE5, allowing increased blood flow to tissues," "The many findings from these Phase III analyses suggest Cialis has the potential to be a valuable treatment for a large number of men who have ED, regardless of severity," and "...Cialis was well tolerated, with generally mild-to-moderate side effects that diminished in frequency with continued treatment." These claims state or imply that IC351, an investigational new drug, is safe or effective for erectile dysfunction.

**Requested Action**

Lilly ICOS should immediately discontinue the websites and all other promotional materials and activities for IC351 that contain the same or similar claims or presentations. We request that Lilly

[1] https://secure.lillyicos.com/news_lev2.cfm
[2] www.icos.com
[3] www.lilly.com

ICOS respond, in writing, with its intent to comply with the above. DDMAC should receive your written response no later than January 17, 2002. This response should list similarly violative materials with a description of the method for discontinuation and the discontinuation date.

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #10598 in addition to the NDA number.

Sincerely,

*{See appended electronic signature page}*

Barbara S. Chong, Pharm.D., BCPS
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

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

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/s/

Barbara Chong
1/3/02 09:42:58 AM

From the Lilly ICOS Newsroom

*This news release was issued in the United States and is intended for use by U.S. journalists. The information contained in this release was current on the date the release was issued and will become outdated over time. Lilly ICOS does not assume any responsibility for updating information in this release.*

## In Two New Studies, Cialis™ (IC351) Provided an Extended Period of Responsiveness In Men With Erectile Dysfunction

*Tuesday, May 1, 2001*

According to results of clinical trials released today on Cialis™, a new PDE5 inhibitor in development by Lilly ICOS LLC to treat erectile dysfunction (ED), men reported an improved ability to achieve erections even 24 hours after taking the drug. These data will be presented for the first time at the 96th Annual Meeting of the American Urological Association in Anaheim, California, in June.

"Cialis has the potential to be a valuable new treatment option for men with ED and their partners," said Dr. Harin Padma-Nathan, urologist and lead investigator of the study. "A therapy that allows a man with ED to engage in intercourse within a 24-hour window permits the couple to regain spontaneity in their sexual relationship."

**Cialis provided extended duration of responsiveness and worked promptly**
In the first of two trials to measure responsiveness, 61 men with mild-to-severe ED were randomized to receive Cialis 10 mg or placebo in a clinical setting. After taking Cialis, men underwent RigiScan™ (a device for measuring the firmness and duration of erections) evaluations during exposure to visual sexual stimulation. Men in the Cialis group were significantly more successful in achieving erections than men in the placebo group, even when evaluated at 24 hours postdosing.

To measure the onset of responsiveness in a more natural setting, 223 men received Cialis (up to 20 mg) or placebo in a second, home-based study. The men were instructed to take the medication immediately before engaging in sexual activity and to use a stopwatch to record the elapsed time until they achieved an erection sufficient for successful intercourse. In this trial, the ability to achieve an erection after sexual stimulation was statistically superior in the group taking Cialis compared with the placebo group at 16 minutes postdosing. Patients on Cialis in this study also recorded statistically significantly more success at second sexual encounters than patients on placebo for a period of up to 24 hours after dosing.

There were no treatment-related serious adverse events. The most commonly reported adverse event was headache. "The side effects in the trials are consistent with other large-scale trials conducted to date with Cialis," said Dr. Padma-Nathan. "Importantly, the extended duration of responsiveness does not appear to increase the rate of side effects or their severity. This is further supported by the fact that very few men chose to discontinue Cialis treatment due to side effects. "Extended duration of responsiveness important to men with ED. Dr. Padma-Nathan said that these results are especially encouraging in light of a recent Harris Interactive survey of 256 men with ED in which 88 percent of the men surveyed indicated the duration of responsiveness was either "very important" or "extremely important" in selecting a treatment.

**Cialis™ Phase II/III Studies Encouraging**
In a previously released Phase II placebo controlled study, Cialis improved erectile function in up to 88 percent of men with varying degrees of ED. In a placebo controlled Phase III study in men

with difficult-to-treat diabetes-related ED, up to 64 percent of men reported improved erections. The trials demonstrated good tolerability over the entire duration of the medication's effect with headache and dyspepsia (upset stomach) the most commonly reported side effects. The reported side effects were transient, generally considered mild to moderate, and their occurrence diminished with continued treatment. In addition, there were no serious treatment related adverse events.

Erectile dysfunction is defined as the consistent inability to attain and maintain an erection sufficient for sexual intercourse. It affects an estimated 152 million men and their partners worldwide with many cases caused by physical conditions, including cardiovascular disease and diabetes.

**About Lilly ICOS**
Lilly ICOS LLC, a joint venture between ICOS Corporation (NASDAQ: ICOS) and Eli Lilly and Company (NYSE: LLY), is developing Cialis, an investigational PDE5 inhibitor.

Eli Lilly and Company, a leading innovation-driven corporation, is developing a growing portfolio of best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs.

ICOS Corporation is a product-driven company that has expertise in both protein-based and small molecule therapeutics. ICOS, located in Bothell, Wash., combines capabilities in molecular, cellular and structural biology, high throughput drug screening, medicinal chemistry and genomics to develop highly innovative products with significant commercial potential. The company applies its integrated approach to specific target areas where it has expertise. ICOS believes this strategy increases the chances of successfully developing commercial products. ICOS' disease targets include erectile dysfunction, female sexual dysfunction, sepsis, pulmonary hypertension and other cardiovascular diseases.

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This press release contains forward-looking statements about the potential of the investigational compound Cialis™ (IC351) in treating male erectile dysfunction that reflect management's current beliefs. However, as with any pharmaceutical under development, there are risks and uncertainties in the process of development and regulatory review. There are no guarantees that future clinical trials will confirm the preliminary results reported in this release or that the product will receive regulatory approvals or prove to be commercially successful. In addition, new pharmaceutical products can face risks of intellectual property claims and product litigation. For further discussion of these and other risks and uncertainties, see the U.S. Securities and Exchange Commission filings of ICOS and Lilly.

**Date:** October 2, 2001

**Refer to:** (317) 277-6738 – Blair Austin (Lilly)
(425) 415-2207 – Lacy Fitzpatrick (ICOS)

**First Presentation of Large-Scale Integrated Analysis of Phase III Data on Cialis™ (tadalafil) Shows Consistent Effect in Men With Erectile Dysfunction**

*New study shows Cialis absorption not affected by food intake*

ROME, ITALY – The first presentation of a large-scale integrated analysis of Phase III data on Cialis™ (tadalafil), a new oral treatment for erectile dysfunction (ED) being developed by Lilly ICOS LLC, shows a consistent response to the investigational treatment. Eighty-one percent of patients treated with 20 mg Cialis (N=165) reported improved erections.[1] This analysis, taken from studies of 972 men with ED (711 Cialis, 261 placebo), and other new research – including a study that shows Cialis's absorption was not decreased by food intake[2] – were presented today at the 4th Congress of the European Society for Sexual and Impotence Research (ESSIR) in Rome.

"With each new data analysis, we continue to see consistent and robust scientific evidence that Cialis has an attractive profile," said Charles Beasley, M.D., medical director, Eli Lilly and Company. "The many findings from these Phase III analyses suggest Cialis has the potential to be a valuable treatment for a large number of men who have ED, regardless of severity. Cialis has other attributes that may also be clinically important."

**Pharmacokinetic Analyses: Key Findings**

Several studies were conducted to evaluate Cialis absorption by the body. Pharmacokinetic studies are important because they can identify differences in drug absorption and elimination in

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[1] Symposium, "Expanding treatment options for male impotence." 4th Congress of the European Society for Sexual and Impotence Research. October 2, 2001.

[2] Patterson, B et al. "The effect of intrinsic and extrinsic factors on the pharmacokinetic properties of tadalafil (IC351)." Poster presentation at the 4th Congress of the European Society for Sexual and Impotence Research. Poster presented 08.00-09.00 October 3, 2001.

the body between various patient populations. These studies investigated, among other characteristics, the impact of age, diabetes, renal function, and liver function on the pharmacokinetics of Cialis™. There were no clinically significant differences in extent of drug exposure among these diverse groups. In addition, Cialis's absorption was not decreased by food intake.[3]

"These findings suggest that dosing for Cialis should be simple and uncomplicated, which is important from a health care professional standpoint," said Hartmut Porst, associate professor of the urological department of the medical university in Bonn, Germany, and secretary general of the ESSIR. "From a patient's point of view, it is the absence of food effect that I find most interesting. These data suggest that a man can have a normal, romantic dinner with his partner without diminishing the effect of Cialis."

**Integrated Phase III Analysis - Key Findings From General and Diabetes Populations**

The integrated Phase III analysis included randomized, placebo-controlled studies involving 972 men with ED of various causes and severity. Men were treated with Cialis (ranging up to 20 mg) or placebo for 12 weeks. Improved erections, as assessed by the Global Assessment Questionnaire (GAQ), were reported by 81 percent of patients taking 20 mg Cialis (35 percent placebo).[4]

The Phase III integrated analysis showed Cialis improved erections in 76 percent of the subset of men with diabetes taking a 20 mg dose[5]. Diabetes-related ED is often more difficult to treat than ED caused by other factors. ED is a common complication of diabetes, affecting between 27 and 75 percent of men with the disease.[6] The World Health Organization estimates 151 million people worldwide have diabetes.[7]

In the Phase III studies, participants were instructed to take study medication at the time of their choosing prior to sexual activity, with no more than one dose daily. No instructions were given with regard to food or alcohol consumption and time of dosing.

**Cialis Period of Responsiveness -- Key Findings**

Two separate studies, presented in Europe for the first time, showed Cialis works for up to

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[3] *Ibid.*

[4] CME symposium, "Expanding treatment options for male impotence." 4th Congress of the European Society for Sexual and Impotence Research. October 2, 2001.

[5] *Ibid.*

[6] Guay A. Treatment of erection dysfunction in men with diabetes. *Diabetes Spectrum 1998;* 11: 2

[7] International Diabetes Federation. *Diabetes Atlas 2000.*

24 hours and as early as 16 minutes after taking the pill[8]. In the first study, 61 men with mild-to-severe ED were randomized to take Cialis™ or placebo and underwent RigiScan® (device for measuring firmness and duration of erections) evaluations during exposure to visual sexual stimulation. Men taking Cialis experienced significantly more success in improvement of erectile function than men in the placebo group, even when evaluated 24 hours after dosing. In the second study, designed to measure the drug's onset, 223 men took Cialis or placebo and used a stopwatch to record the elapsed time until they achieved an erection sufficient for intercourse. The ability to achieve an erection (with sexual stimulation) was statistically superior in the group taking Cialis 20 mg, compared with the placebo group, at 16 minutes after dosing, and the majority of men taking Cialis were able to respond within 30 minutes.

"This period of responsiveness may be an important attribute for emerging ED treatments, as it may enable a man and his partner to have sex whenever they choose within a 24-hour period," Professor Porst said.

**Side Effects**

Throughout the Phase III trials, Cialis was well tolerated, with generally mild-to-moderate side effects that diminished in frequency with continued treatment. The most commonly reported side effects throughout the Phase III trials were headache, upset stomach, backache, muscle aches, flushing and nasal congestion. The discontinuation rate due to side effects in these trials was comparable to that with placebo.

Cialis is currently under review for marketing approval by the European Agency for the Evaluation of Medicinal Products (EMEA) and the US Food and Drug Administration (FDA).

Erectile dysfunction is defined as the consistent inability to attain and maintain an erection sufficient for sexual intercourse. It affects an estimated 152 million men and their partners worldwide with many cases caused by physical conditions, including cardiovascular disease and diabetes.[9] In Europe, approximately 31 million men suffer from ED.[10]

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[8] Padma-Nathan, H. "Tadalafil (IC351) provides prompt response and extended period of responsiveness for the treatment of men with ED." Poster presentation at the 4th Congress of the European Society for Sexual and Impotence Research. Poster presented 08.00-09.00 October 1, 2001.

[9] Aytac et al. The Likely Worldwide Increase in Erectile Dysfunction Between 1995 and 2025 and Some Possible Policy Consequences. *BJU International.* 1999; 84:50-56.

[10] *Ibid.*

**About Lilly ICOS**

Lilly ICOS LLC, a joint venture between ICOS Corporation (NASDAQ: ICOS) and Eli Lilly and Company (NYSE: LLY), is developing Cialis™, which is currently under investigation for the treatment of sexual dysfunction.

Eli Lilly and Company, a leading innovation-driven corporation, is developing a growing portfolio of best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers – through medicines and information – for some of the world's most urgent medical needs.

ICOS is a product-driven company that has expertise in both protein-based and small molecule therapeutics. ICOS combines its capabilities in molecular, cellular and structural biology, high throughput drug screening, medicinal chemistry and gene expression profiling to develop highly innovative products with significant commercial potential. ICOS applies its integrated approach to specific target areas where it has expertise. ICOS believes its strategy of targeting multiple therapeutic areas by developing drugs that act through distinct molecular mechanisms increases its chances of successfully developing commercial products.

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This press release contains forward-looking statements about the potential of the investigational compound Cialis (tadalafil) in treating male erectile dysfunction that reflect management's current beliefs. However, as with any pharmaceutical under development, there are risks and uncertainties in the process of development and regulatory review. There are no guarantees that future clinical trials will confirm the preliminary results reported in this release or that the product will receive regulatory approvals or prove to be commercially successful. For further discussion of these and other risks and uncertainties, see the U.S. Securities and Exchange Commission filings of ICOS and Lilly.

**Cialis** (IC351)

[redacted]

**Status:**
Erectile dysfunction: FDA Application

Erectile dysfunction (ED) affects as many as 70 million men in North America and Europe. Following sexual stimuli, Cialis relaxes blood vessels by inhibiting the enzyme PDE5, allowing increased blood flow to tissues.

More than 50 Phase 1, 2 and 3 clinical trials have been conducted with Cialis. Integrated Phase 3 data were reported at the European Society for Sexual and Impotence Research meeting on October 2, 2001 (see Company press release for results). Lilly ICOS LLC filed the NDA on Cialis in the U.S., Europe and other countries around the world.