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Multiple Clinical Trial Analysis Shows Duloxetine Reduces Stress Urinary Incontinence Episodes and Improves Quality of Life for Women

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Data presented today at the third International Consultation on Incontinence, provide evidence for the efficacy of duloxetine, an investigational agent for the treatment of women with stress urinary incontinence (SUI). Stress urinary incontinence is an embarrassing and bothersome medical condition, which affects nearly 15 million adult women in the United States^{1,2,3} and can have a significant impact on quality of life. Results from a worldwide, four-study meta-analysis, comparing the efficacy of duloxetine and placebo in more than 1,900 women, demonstrated a statistically significant improvement after 12 weeks, compared to placebo ($p < 0.001$). This improvement was evident in a number of analyses including the reduction in frequency of incontinence episodes and the improvement in the quality of life scores.⁴

SUI is the accidental leakage of urine during physical activities such as sneezing, coughing, laughing, lifting or exercising. With nearly twice the prevalence of urge incontinence, SUI is the most common form of urinary incontinence among women.^{1,5} Although common, SUI is a medical condition that is not normal at any age, but unfortunately many women do not seek treatment because they are embarrassed, fear surgery, or believe it is a normal part of aging and that nothing can be done about it. The primary causes of SUI are weakness of the urethral sphincter and/or diminished pelvic support of the bladder and urethra. Risk factors include obesity, chronic coughing, constipation and childbirth.⁶

Speaking at the International Consultation on Incontinence, Professor van Kerrebroeck, University Hospital, Maastricht, Netherlands, said: "Although common, SUI is not normal at any age and has a profoundly negative impact on a woman's quality of life."

The results come from a meta-analysis of four double-blind, placebo-controlled studies, which enrolled a total of 1,913 women at 186 study sites in North America, Europe, South America, Africa and Australia. Patients were studied for 12 weeks, followed by an open-label extension period.⁴

The results from the double-blind studies show that approximately two thirds of women reported feeling better at three months, as measured by Patient Global Impression of Improvement scores (PGI-I). During the double-blind and open-label studies, 82 percent of women who continued for one year on duloxetine considered themselves better. Further results demonstrate that, at 12 weeks, statistically greater improvements were seen with the duloxetine arm compared to placebo ($p < 0.001$) in a number of analyses, including:⁴

- Incontinence Episode Frequency (IEF) median decreased 52 percent (duloxetine) versus 33 percent (placebo)
- Incontinence Quality of Life (I-QOL) scores improved +9.2 points (duloxetine) versus +5.9 points (placebo).

The I-QOL questionnaire comprised three subscales, which include avoidance/limiting behavior, psychosocial impact and social embarrassment. Each showed a statistically significant improvement with duloxetine compared to placebo ($p < 0.001$). I-QOL is measured using a patient-completed questionnaire where scores are totaled to evaluate impact on quality of life. A greater increase over baseline score demonstrates a greater improvement in QOL. This meta-analysis showed that women on duloxetine consistently had a greater improvement in quality of life assessments, as measured by the I-QOL.

Clinical studies of duloxetine in SUI have shown the most commonly reported adverse events (incidence of $\geq 5\%$ and at least twice the placebo rate) reported by patients receiving duloxetine to have been: nausea, fatigue, dry mouth, insomnia, constipation, dizziness, and somnolence.⁷

Duloxetine is a balanced dual reuptake inhibitor of the neurotransmitters serotonin and norepinephrine,⁸ which play a key role in normal urethral sphincter closure, the weakening of which can result in SUI. By increasing neurotransmitter concentration,

duloxetine is believed to increase the tone and contraction of the urethral sphincter,⁹ which helps prevent accidental urine leakage during physical activities such as coughing, sneezing, laughing, lifting or exercise.

About Yentreve™ *

Yentreve™ (duloxetine hydrochloride) is a balanced potent dual reuptake inhibitor of the neurotransmitters serotonin and norepinephrine based on pre-clinical studies⁸. Yentreve is believed to affect SUI by blocking the reuptake of serotonin and norepinephrine in the spinal cord, and the increase in the neurotransmitters in turn stimulates increased activity of the nerve that stimulates the urethral sphincter.⁹ This stimulation is believed to increase contraction of the urethral sphincter at the opening of the bladder, thereby helping prevent accidental urine leakage with physical activity.

The U.S. Food and Drug Administration issued an approvable letter for Yentreve in September 2003.

About Eli Lilly and Boehringer Ingelheim

In November 2002, Eli Lilly and Company and Boehringer Ingelheim signed a global long-term agreement to jointly develop and commercialize duloxetine hydrochloride for the treatment of stress urinary incontinence (SUI), depression and diabetic neuropathic pain. This partnership covers most countries worldwide with few exceptions. In the U.S., the collaboration focuses on SUI.

About Eli Lilly and Company

Lilly, a leading, innovation-driven corporation, is developing a growing portfolio of first-in-class and 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 leading urgent medical needs. Additional information about Lilly is available at www.lilly.com.

About Boehringer Ingelheim Pharmaceuticals, Inc.

Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, Conn., is the largest U.S. subsidiary of Boehringer Ingelheim Corporation (Ridgefield, Conn.) and a member of the Boehringer Ingelheim group of companies.

The Boehringer Ingelheim Corporation is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 152 affiliates in 45 countries and more than 34,000 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine.

In 2003, Boehringer Ingelheim posted net U.S. sales of \$8.37 billion (7.4 billion euro) while spending more than one fifth of net sales in its largest business segment--prescription medicines--on research and development.

For more information please visit www.boehringer-ingelheim.com.

This press release contains forward-looking statements about the potential of duloxetine for the treatment of stress urinary incontinence and reflects Lilly's current beliefs. However, as with any pharmaceutical product under development, there are substantial risks and uncertainties in the process of development and/regulatory review. There is no guarantee that the product will receive regulatory approvals and any indication for which it is approved will be determined at the discretion of the Food and Drug Administration. There is also no guarantee that the product will prove to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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* Yentreve is a trademark of Eli Lilly and Company. This trademark is pending approval by the FDA as a proprietary drug name for the established name, duloxetine hydrochloride.