



August 13, 2004

## **Yentreve Receives Approval Across the European Union for the Treatment of Stress Urinary Incontinence in Women**

*August 13, 2004*

Eli Lilly and Company and Boehringer Ingelheim announced today that Yentreve<sup>TM</sup>\* (duloxetine hydrochloride) has been granted marketing authorization across the European Union (EU) for the treatment of moderate to severe stress urinary incontinence (SUI) in women.

SUI is the accidental leakage of urine during physical activities such as sneezing, coughing, laughing, lifting or exercising, and it affects nearly 15 million American adult women.<sup>1,2,3</sup> With nearly twice the prevalence as urge incontinence, SUI is the most common form of urinary incontinence among women.<sup>1,4</sup>

Although common, SUI is a medical condition that is not normal at any age; 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, childbirth, chronic coughing and constipation.<sup>5</sup>

Yentreve<sup>TM</sup>\* is a balanced dual reuptake inhibitor of the neurotransmitters serotonin and norepinephrine<sup>6</sup> and is currently being evaluated by the U.S. Food and Drug Administration (FDA) for the treatment of SUI. The FDA issued an approvable letter for Yentreve<sup>TM</sup>\* in August 2003. Lilly and Boehringer Ingelheim have recently submitted a complete response to the FDA and anticipate approval from the agency for Yentreve in the first half of 2005.

"With the EU approval of Yentreve<sup>TM</sup>\*, Lilly and Boehringer Ingelheim are excited to soon be offering patients in Europe the first medication indicated for the specific symptoms of SUI -- a distressing and embarrassing medical disorder that affects millions of women worldwide," said Dr. Tim Garnett, group medical director, Eli Lilly and Company.

"The proven reduction of incontinence episodes demonstrated in clinical studies and the statistically significant improvement in quality of life shown in women treated with Yentreve<sup>TM</sup>\* make this new oral medication an effective and well tolerated treatment option for the many women living with SUI," said Manfred Haehl, M.D., corporate medical director, Boehringer Ingelheim. "We are very pleased that The European Agency for the Evaluation of Medicinal Products has acknowledged the importance of this novel medication, which we can now offer to SUI patients throughout Europe."

### **About Yentreve<sup>TM</sup>\***

Yentreve<sup>TM</sup>\* (duloxetine hydrochloride) is a balanced dual reuptake inhibitor of the neurotransmitters serotonin and norepinephrine based on preclinical studies.<sup>6</sup> Yentreve<sup>TM</sup>\* 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 pudendal nerve that controls the external urethral sphincter.<sup>7</sup> This stimulation is believed to increase contraction of the external urethral sphincter, thereby helping prevent accidental urine leakage with physical activity.

Clinical studies of Yentreve<sup>TM</sup>\* have shown the most commonly reported adverse events (incidence of > 5 percent and at least twice the placebo rate) reported by patients receiving duloxetine have been nausea, dry mouth, fatigue, insomnia, constipation, headache, dizziness, somnolence (drowsiness) and diarrhea.<sup>8</sup>

### **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.

**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, IN, Lilly provides answers-through medicines and information-for some of the world's most urgent medical needs. Additional information about Lilly is available on [www.lilly.com](http://www.lilly.com).

### **Boehringer Ingelheim Pharmaceuticals, Inc.**

Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, CT, is the largest U.S. subsidiary of Boehringer Ingelheim Corporation (Ridgefield, CT) 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](http://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.*

---

\* 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.

1. Hampel C, Wienhold D, Benken N, Eggersmann C, Thuroff T. Definition of overactive bladder and epidemiology of urinary incontinence. *Urology*. 1997;50(suppl 6A):4-14.
2. Diokno A, Burgio K, Fultz N, Kinchen K, Obenchain R, and Bump R. Medical and self-care practices reported by women with urinary incontinence. *Am J Managed Care*. 2004;10:69-78. *The estimate of STRESS URINARY INCONTINENCE prevalence was derived from Diokno et al and based on STRESS URINARY INCONTINENCE prevalence as determined by Hampel et al and by Diokno et al.*
3. US Census 2000 Briefs (Age & Gender), US Department of Commerce website.
4. Fultz NH, Burgio K, Diokno A, Kinchen K, Obenchain R and Bump R. Burden of stress urinary incontinence for community-dwelling women. *Am J Obstet Gynecol*. 2003; 189: 1275-1282.
5. Bump R, Norton P. Epidemiology and natural history of pelvic floor dysfunction. *Obstet Gynecol Clin North Am*. 1998; 25(04): 723 - 746.
6. Bymaster F, Dreshfield-Ahmad L, Threlkeld P, Shaw J, Thompson B, Nelson D, et. al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, Human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology*. 2001; 25(6):871-880.
7. Thor K, Katofiasc M. Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized female cat. *J Pharmacol Exp Ther*. 1995; 274:1014-1024.
8. Hurley D, Turner C, Baygani S, Yalcin I and Viktrup L. Duloxetine for stress urinary incontinence: A meta-analysis of safety. Poster presented at the International Federation of Gynaecology and Obstetrics (FIGO) World Congress, Santiago, Chile. 2-7 November 2003.