In New Study, Duloxetine Was Equally Effective, Regardless of Switch Method, In Reducing Painful Symptoms in SSRI Non- or Partial-responders with Depression

SAN DIEGO, May 24, 2007 (PR Newswire Europe via COMTEX News Network) -- The antidepressant duloxetine hydrochloride was equally effective in reducing painful symptoms in depressed patients who did not respond, or responded only partially, to treatment with a selective serotonin reuptake inhibitor (SSRI), regardless of whether those patients were switched from an SSRI abruptly or gradually.(1) This new data was presented today at the American Psychiatric Association's 160th Annual Meeting in San Diego, Calif.

(Logo: http://www.newscom.com/cgi-bin/prnh/20031219/LLYLOGO)

(Logo: http://www.newscom.com/cgi-bin/prnh/20040122/BILOGO)

Between 30-50 percent of individuals treated with a given antidepressant do not respond to that treatment.(2,3) As a result, physicians often need to switch patients from one antidepressant to another. Although this is a common clinical scenario, there are relatively few published studies to guide physicians on how to switch patients from one antidepressant to another.

"Recent data suggests the more antidepressants an individual has tried, the less likely they are to benefit from a new antidepressant.(4) Therefore it is important to maximise the chance of remission earlier in the treatment pathway," said Prof. Angel L. Montejo, Psychiatry Research Coordinator, University Hospital of Salamanca, Spain. "These results demonstrate that a switch to duloxetine results in a significant decrease in the painful symptoms in patients with depression and was well tolerated regardless of the switch method used."

The new results are based on several secondary endpoints from a study comparing the efficacy, safety and tolerability of two switch methods in 368 patients who remained depressed despite taking an SSRI for at least six weeks.(5) Participants were randomized to either abrupt discontinuation of their SSRI (the Direct Switch, or DS group) or to a gradual/tapered discontinuation of their SSRI (the Start-Taper Switch, or STS group). Both groups began taking duloxetine 60 mg/day at the beginning of the study. The dosage could be increased to a maximum of 120 mg/day based on the investigator's discretion.(1)

The primary data disclosure took place at a major medical conference in December 2006.(5) The primary objective of the overall study was to demonstrate the non-inferiority of Direct Switch (DS) compared with Start-taper Switch (STS) based on changes in HAMD17 total scores. Overall, that initial data disclosure showed that switch to duloxetine was associated with significant improvements in the emotional symptoms of depression, and was well tolerated and safe, regardless of which SSRI the patient was taking at study entry.

This new analysis focused on the prevalence and severity of painful symptoms following the switch to duloxetine and in relation to switch method. The study participants, as a group, had average pain scores indicating clinically significant physical pain. Ten weeks after switching to duloxetine, patients made significant improvements on all pain measures evaluated, regardless of which switch method was used.(1)

Efficacy, safety, and tolerability outcomes following Direct Switch (DS) from SSRI to duloxetine were similar to those observed for Start-taper Switch (STS). The most commonly reported adverse events in the study were headache (13.1 percent for DS vs. 9.7 percent STS), dry mouth (10.4 percent DS vs. 11.9 percent STS), and nausea (8.2 percent DS vs. 8.1 percent STS). No adverse event was reported by significantly more patients in one group compared with the other. An excess of adverse events was not evident following switch from any particular SSRI.(1)

"This study provides some much-needed clinical evidence to help physicians successfully switch patients from one antidepressant to another when they remain depressed," Montejo said. "It also highlights the continued prevalence and severity of painful symptoms among patients who are not adequately responding to SSRI therapy," he said.

Duloxetine, a member of a class of drugs commonly referred to as serotonin and norepinephrine reuptake inhibitors (SNRI)(6), is approved in more than 70 countries for the treatment of major depression.

There is a possibility of an increased risk of suicidal thoughts or behaviour in children and young adults treated with antidepressants. Patients should call their doctor right away if they experience worsening depression symptoms, unusual

changes in behaviour or thoughts of suicide, especially at the beginning of treatment or after a change in dose.

Notes to Editors:

About the Study(1)

Methodology

Subjects were outpatients who met criteria for MDD despite having taken an SSRI antidepressant for at least 6 weeks, and who had a Hamilton Depression Rating Scale (HAMD17) total score of >/=15 and a Clinical Global Impression of Severity (CGI-S) score of >/=3. Eligible patients were randomized to either abrupt discontinuation of their SSRI immediately followed by initiation of duloxetine (Direct Switch) or to tapered discontinuation of their SSRI over 2 weeks and simultaneous administration of duloxetine (Start-taper Switch). Painful physical symptoms were assessed at baseline and at the 10-week study endpoint via a variety of measures including 6 Visual Analogue Scales (VAS) for pain, and the Symptom Questionnaire-Somatic Subscale (SQ-SS).

Results included: (1)

- Clinically significant levels of pain (mean baseline VAS scores >30 mm) were seen across all VAS pain measures prior to switching.
- Switch to duloxetine resulted in significant improvements on all pain measures in both treatment groups.
- Mean improvements in each of the VAS pain scores, expressed as a percentage of baseline VAS scores for the Direct-Switch and Start-Taper-Switch groups respectively, were:
  - Overall Pain 20.3 percent, 17.9 percent;
  - Headache 25.6 percent, 15.6 percent;
  - Back Pain 18.2 percent, 20.2 percent;
  - Shoulder Pain 17.9 percent, 16.2 percent;
  - Interference with Daily Activities 29.5 percent, 23.2 percent;
  - Time in Pain While Awake 28.8 percent, 26.3 percent.

Efficacy, safety, and tolerability outcomes following direct switch from SSRI to duloxetine were similar to those observed for start-taper switch. Few patients experienced a serious adverse event (5 patients during the 10 weeks of treatment and 1 during the taper period), and there was a low rate of discontinuations due to adverse events (6.6 percent DS vs. 3.8 percent STS).

This was an open-label study, so biases inherent in open-label studies could have been a factor in the observed outcomes. Due to the large number of possible SSRI/dose possibilities for patients entering the study, it was necessary for study investigators to use their clinical judgment to devise an appropriate 2-week down-titration regimen for patients in the STS group. Although general guidance was provided to investigators within the study protocol, the taper was nevertheless not rigidly standardized.

About Duloxetine

While duloxetine's mechanism of action in humans is not fully known, it is believed to affect both serotonin and norepinephrine/noradrenaline mediated nerve signalling in the brain and the spinal cord. Based on pre-clinical studies, duloxetine is a balanced and potent reuptake inhibitor of serotonin and norepinephrine/noradrenaline. Scientists believe its effect on pain perception is due to increasing the activity of serotonin and norepinephrine in the central nervous system.

Duloxetine is approved for the treatment of depression and diabetic peripheral neuropathic pain in many countries and is approved in some countries for the treatment of stress urinary incontinence. Duloxetine is approved only for adults 18 and over. There is a possibility of an increased risk of suicidal thoughts or behaviour in children and young adults treated with antidepressants. Patients should call their doctor right away if they experience worsening depression symptoms, unusual changes in behaviour or thoughts of suicide, especially at the beginning of treatment or after a change in dose.

Patients taking Cymbalta may experience dizziness or fainting upon standing. The most common side effects of Cymbalta include:

- For depression: Nausea, dry mouth, headache, insomnia, diarrhea
  - For diabetic peripheral neuropathic pain: Nausea, somnolence (sleepiness), fatigue, headache, dizziness
  - For stress urinary incontinence: Nausea, dry mouth, fatigue

This is not a complete list of side effects.

Duloxetine is contraindicated in patients who are allergic to it, who have liver disease resulting in hepatic impairment, who are taking a monoamine oxidase inhibitor (MAOI), fluvoxamine, ciprofloxacin or enoxacine or who have severe kidney disease. The initiation of treatment with duloxetine also is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.

About Depression

Major Depressive Disorder (MDD) affects approximately 121 million people worldwide.(7) The World Health Organization estimates depression will be among the highest-ranking causes of disability in developed countries by 2020, second only to ischemic heart disease worldwide.(8) It can happen to anyone of any age, race or ethnicity; however, women are nearly twice as likely to experience depression as men.(9) Although it is one of the most frequently seen psychiatric disorders in the primary care setting,(10,11) it often goes undiagnosed or is under-treated.(7,12) This might be because depressed people often present with physical symptoms rather than emotional complaints; in one large study, 69 percent of patients with MDD reported only physical symptoms as the reason for visiting their physician.(13)

Complete elimination of symptoms, or remission, is the primary goal of depression treatment. Treating the full spectrum of emotional and physical symptoms to remission significantly decreases a patient's risk of relapse.(14)

Eli Lilly and Company and Boehringer Ingelheim

In November 2002, Eli Lilly and Company and Boehringer Ingelheim signed a long-term agreement to jointly develop and commercialize duloxetine hydrochloride. This partnership covers neuroscience indications in most countries outside of the United States and Japan, with few exceptions.

About Eli Lilly and Company

Lilly, 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.

About Boehringer Ingelheim

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 137 affiliates in 47 countries and 38,400 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 2006, Boehringer Ingelheim posted net sales of 10.6 billion euro while spending 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.

P-LLY

Duloxetine for depression and diabetic peripheral neuropathic pain is marketed by Lilly and Boehringer Ingelheim in all countries included in the partnership under the brand name Cymbalta, except for Greece, Italy and Spain. In Greece, Italy and Spain Lilly markets the product as Cymbalta and Boehringer Ingelheim markets the product as Xeristar(R). In the United States, Cymbalta is marketed by Lilly and Quintiles. In Japan, duloxetine will be co-developed and co-marketed by Lilly and Shionogi & Co., Ltd.

Duloxetine for stress urinary incontinence is marketed by Lilly under the brand name Yentreve.(R)

References:

(1) Perahia, DGS, Quail, D, Desaiah D, Montejo, A-L. Switch to Duloxetine in SSRI non- and partial-responders: Effects on painful physical symptoms of depression. Presented at the American Psychiatric Association 160th Annual Meeting, San Diego, 23 May 2007

(2) Baghai, TC., Moller, HJ, Rupprecht, R. (2006) Recent progress in pharmacological and non-pharmacological treatment options of major

depression. Curr Pharm Des. ;12(4):503-15.
(3) Ruhe HG, Huyser J, Swinkels JA, Schene AH. (2006) Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. J Clin Psychiatry. Dec;67(12):1836-55.
(4) Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg A, Stewart JW, et al (2006). Acute and Longer-term Outcomes in Depressed Outpatients Who Required One or Several Treatment Steps: A STAR D Report. Am J of Psych Oct; 163(11):1905-1917
(5) Perahia, DGS, Quail, D, Desaiah D, Rasmussen K. Switching to Duloxetine From Other Antidepressants: A Regional Multicenter Trial Comparing Two Switching Techniques. Presented at the American College of Neuropsychopharmacology45th Annual Meeting, Hollywood, FL December 2006
(6) Bymaster, FP et al. "The Dual Transporter Inhibitor Duloxetine: A Review of its Preclinical Pharmacology, Pharmacokinetic Profile, and Clinical Results in Depression." Current Pharmaceutical Design. 2005; 11: 1475-1493.
(7) World Health Organization. Factsheet - Depression, 2005. Available at: http://www.who.int/mental_health/management/depression/definition/en/. Last visited 26 April 2007
(8) Murray CJL, Lopez AD, eds. The Global Burden of Disease; 1996.
(9) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., Text Revision. Washington DC: American Psychiatric Association; 2000:345-428.
(10)Ormel J, et al. Common mental disorders and disability across cultures: results from the WHO Collaborative Study on Psychological Problems in General Health Care. JAMA. 1994;272:1741-1748.
(11)Spitzer RL, et al. Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study. JAMA. 1994;272:1749-1756.
(12)Ormel J, Koeter MWJ, van den Brink W, van de Willige G. Recognition, management, and course of anxiety and depression in general practice. Arch Gen Psychiatry. 1991;48:700-706.
(13)Simon GE et al. An International Study of the Relation Between Somatic Symptoms and Depression. New Engl J Med. 1999;341(18):1329-35.
(14)Paykel ES, et al. Psychol Med. 1995;25(6):1171-1180.

David J. Shaffer of Eli Lilly and Company, +1-317-651-3710; or Ute E. Schmidt of Boehringer Ingelheim, +49-6132-77-97296; Photo: NewsCom: http://www.newscom.com/cgi-bin/prnh/20031219/LLYLOGO, NewsCom: http://www.newscom.com/cgi-bin/prnh/20040122/BILOGO, PRN Photo Desk, photodesk@prnewswire.com