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Lilly's New Pill For Depression Reopens Debate

By Leila Abboud

THIS SUMMER, drug maker **Eli Lilly** & Co. plans to storm the nearly $17 billion worldwide market for antidepressants with a new drug called Cymbalta.

With its launch, the pharmaceutical giant will reignite an ongoing scientific debate about how to treat depression: Is it better to attack one brain receptor or two? Cymbalta's debut also may spur discussions about how far companies can go in promoting this new class of antidepressants.

Lilly says Cymbalta works better than the dominant type of drugs in use because it not only boosts serotonin levels in the brain, much like Lilly's own Prozac, but also acts on a second brain chemical, norepinephrine, also thought to be linked to depression. The Food and Drug Administration is expected to approve Cymbalta (pronounced sim-balta) this summer.

Scientific research, however, into whether dual-action antidepressants like Cymbalta are superior to other medications is inconclusive. "There is some skepticism out there about the dual-action agents and I think there should be," says Alan Schatzberg, a Stanford University professor who consults for Eli Lilly and conducted late-phase Cymbalta trials himself. Before drawing conclusions about the drugs, Dr. Schatzberg wants to see more comprehensive testing, perhaps from the National Institutes of Health.

The buzz around dual-action drugs is a turnaround from the 1990s, the heyday of Prozac. At that time, companies touted the "selectivity" of the new Prozac class of antidepressants, called "selective serotonin reuptake inhibitors." The argument was that SSRIs were better because they hit only one brain receptor, unlike older antidepressants that worked shotgun style, attacking several parts of the brain at once.

While scientists don't fully understand how antidepressants affect the brain, they do have hypotheses about the role of various neurotransmitters in depression. The brain chemical serotonin is believed to affect mood and anxiety, norepinephine is important to energy, and dopamine is involved in attention and feelings of pleasure. Once these neurotransmitters get out of whack, goes the theory, symptoms such as sadness and lethargy can develop. Some drug companies are now tinkering with formulas that target all neurotransmitters.

Wyeth had been the lone voice touting dual-

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action treatments as superior. Its drug Effexor took about six years to gain traction, and faced marketing hurdles along the way. In March, for example, the FDA notified Wyeth that its superiority claims made in medical journals and on radio spots were unsupported. Wyeth stopped the ads. Today, Effexor has $2.7 billion in world-wide annual sales.

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Although Lilly hasn't disclosed its marketing plans for Cymbalta, they are likely to be aggressive. Specifically, the Indianapolis-based company plans to make a case directly to psychiatrists that its dual-action drug can help more depression sufferers achieve "remission," or full recovery.

Despite the ubiquity of modern antidepressants, only half of patients are said to "respond" to treatment; that means they see a 50% improvement, according to measures used in clinical trials, but still may have serious symptoms. Even fewer patients reach remission, a state in which symptoms mostly disappear and medication may, in some cases, be stopped.

Another key part of Lilly's strategy for Cymbalta will be to remind doctors and patients about the physical symptoms of depression, such as chronic aches and pains. "It's clear that we've really missed a big part of the picture on depression" by focusing solely on the mental symptoms, says Michael Detke, Lilly's medical director for Cymbalta.

The company is studying Cymbalta's effect on pain associated with other diseases, and may apply for FDA approval to market the drug as a pain medication. So far, Lilly has funded several continuing-education courses for doctors on the link between depression and pain and already has a provocative pitch: "What four little words could give your patients with depression a better chance to achieve remission?" The answer: "Where does it hurt?"

Cymbalta debuts at a time when several competitors are losing their patent protection—a situation that may amplify the new drug's marketing voice. Pfizer Inc.'s patent for Zoloft expires in 2006, while Effexor will similarly go generic in 2008. Celexa, from Forest Laboratories Inc., also may be available under different brand names as early as 2005 depending on the outcome of patent litigation. Once drugs go off patent, sales of the branded versions typically plummet and ad campaigns behind them usually dry up.

The scientific literature on whether Cymbalta and other dual-action antidepressants are superior to their SSRI predecessors is sparse and contradictory. Lilly and Wyeth cite so-called pooled analyses of clinical trial data. The data, culled from separate drug studies, show the dual-action drugs have higher remission rates than SSRIs. Michael Thase of the University of Pittsburgh—who consults for both Lilly and Wyeth—found that remission rates after eight weeks for Effexor were 45%, compared with 35% for SSRIs and 25% on placebo. For trials involving Cymbalta, Dr. Thase found similar results.

It would take a single, large trial to settle the question of efficacy "once and for all," says P. Murali Doraiswamy, a psychiatrist at Duke University who consults for drug makers including Lilly. But drug companies rarely sponsor definitive head-to-head tests for fear their medicine could come out the loser.