Panel Approves Duloxetine for Lower Back Pain

BY ELIZABETH MECHCATIE

FROM THE FDA'S ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE

BETHESDA, MD. — In a split vote, a Food and Drug Administration advisory panel voted 8-6 that the approved pain indications for duloxetine be expanded to include a broader population of patients with chronic pain.

However, in separate votes, the panel specifically recommended approving the drug for chronic low back pain but not for management of chronic pain from osteoarthritis.

The two adult patient populations considered for the expanded approval, based on data from five clinical studies submitted by duloxetine manufacturer, Eli Lilly & Co., were for those with chronic low back pain and those with chronic pain related to osteoarthritis.

Those voting in favor said they believed the drug could be a valuable treatment for patients with these conditions; those who did not support approval cited concerns that included questions about the strength of the studies.

But in two other separate votes, the panel split on whether the data from the 12- to 13-week clinical trials in the two groups of patients provided adequate evidence of efficacy for the two indications. The panel voted 8-5 with 1 abstention that the clinical data provided enough evidence that duloxetine was effective in managing chronic low back pain. Most of the panelists were not convinced by the data on the osteoarthritis pain indication, voting 9-4 with 1 abstention, that the two studies in OA patients did not provide adequate evidence that duloxetine was an effective treatment for chronic pain due to osteoarthritis—largely because only one of the studies found that treatment was significantly more effective in alleviating pain, compared with placebo.

The panelists also voted 9-4, with 1 abstention, against approving the drug for chronic OA pain, citing inadequate evidence of its efficacy.

Eli Lilly markets duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), as Cymbalta. It was previously approved for pain associated with diabetic peripheral neuropathy (2004) and fibromyalgia (2008). It was first approved in 2004 for major depressive disorder, and also approved for generalized anxiety disorder (2007).

Eli Lilly representatives maintained that duloxetine can provide pain relief via a mechanism that is different from opioids and NSAIDs, and that the efficacy of duloxetine in the studies of patients with OA and chronic low back pain was "at least comparable" with existing therapies.

In the three studies of about 1,000 patients with chronic low (nonradicular) back pain (median age, 51-54 years), average pain severity decreased more in those on 60 mg or 120 mg of duloxetine in all three studies, compared with placebo; the difference was significant in two of the studies. In the two studies of almost 500 patients with osteoarthritis (median age, 62-63 years), intensity of pain decreased more in those on duloxetine, compared with placebo, but the difference was significant only in one study, in which patients were allowed to stay on NSAIDs and acetaminophen.

No new safety issues, other than those already included in the label, surfaced during the studies. Duloxetine can cause increases in aminotransferase levels, and a statement added to the label's warnings and precautions section when the drug was approved for fibromyalgia in 2008 notes there have been reports of hepatoxicity, sometimes fatal, in patients treated with duloxetine and recommends treatment be stopped in patients who become jaundiced or have other signs of clinically significant liver dysfunction.

The potential for hepatoxicity was the main safety issue reviewed by the panel. It voted 9-4 that the drug's safety profile and overall risk-benefit profile supported expanding the approval.

All but two of the panelists did not believe there was evidence that the 120-mg dose was more effective than the 60-mg dose, largely because there were not enough data on the higher dose.

The FDA usually follows the recommendations of its advisory panels. Panelists have been cleared of potential conflicts related to the topic of the meeting, although in some cases, a waiver is granted to a panelist. ■

Sodium Oxybate Voted Down As Treatment for Fibromyalgia

BY ELIZABETH MECHCATIE

FROM THE FDA'S ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT COMMITTEE

BETHESDA, MD. — Advisers to the Food and Drug Administration voted 20-2 that the risk-benefit profile of sodium oxybate did not support approval of the sedative-hypnotic drug as a treatment for fibromyalgia, citing concerns that included the lack of long-term data and the potential for illicit use of the drug.

At a joint meeting, panelists generally agreed the data from clinical trials showed that sodium oxybate, which is approved for treating cataplexy and daytime sleepiness associated with narcolepsy, was effective in treating fibromyalgia. They said the effect was modest, and that treatment may benefit only a subset of patients. They also said it was unclear whether the results could be generalized to the typical fibromyalgia population and that more studies were needed, including those directly comparing sodium oxybate with other treatments for the disorder—milnacipran (Savella), pregabalin (Lyrica), and duloxetine (Cymbalta).

Sodium oxybate is the sodium salt of gamma hydroxybutyrate, an endogenous neurotransmitter synthesized from gamma aminobutyric acid, and is also known as the "date rape" drug. It was approved in an oral solution in 2002 for narcolepsy and has been marketed as Xyrem by Jazz Pharmaceuticals, with a risk evaluation and mitigation (REMS) program that tightly controls distribution of the drug.

The panelists' and FDA reviewers' main concern was that if the drug were approved for fibromyalgia, its use would increase substantially and its availability as a street drug could also increase, despite the controlled distribution.

They were strongly against the company's proposal to use a different commercial name (Rekinla), concentration, and dose. They also opposed a different REMS for the fibromyalgia indication, which they said was confusing and would increase the likelihood of medication errors.

The company proposed that patients would take two doses, one before going to sleep and the second in the middle of the night, which was also cited as a disadvantage for patients.

In two phase III randomized, double-blind, controlled 14-week studies, two different doses of sodium oxybate were compared with placebo in about 1,000 fibromyalgia patients aged 18 and older, who discontinued opiates, benzodiazepines, muscle relaxants, and other medications or devices. A significantly greater proportion of those on sodium oxybate (36%-46%) met the primary end point, at least a 30% reduction in pain from baseline to the end of treatment, compared with placebo (20%-27%). Adverse events were similar to those observed in Xyrem trials.

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Obesity, Inactivity Linked to Increased Fibromyalgia Risk

BY JENNIE SMITH

FROM THE JOURNAL ARTHRITIS CARE AND RESEARCH

Being overweight or obese is associated with a woman's higher risk of developing fibromyalgia, as is lack of exercise.

"Regular physical exercise … may serve as a buffer against the perpetuation of musculoskeletal symptoms that eventually lead to the development of [fibromyalgia]," investigators at the Norwegian University of Science and Technology in Trondheim hypothesized. "However, the results of this study do not indicate a strong effect of physical exercise" on development of the disorder.

Links between obesity and fibromyalgia have been described, Paul J. Mork, Ph.D., and colleagues noted, though the reasons for such associations are not well understood. Fibromyalgia and obesity share characteristics, such as elevated serum levels of certain proinflammatory cytokines.

The investigators used data from the Nord-Trøndelag Health study, a two-part, government-sponsored cohort conducted between 1984 and 1986, and again between 1995 and 1997. They identified 15,990 women 20 years and older who initially reported no fibromyalgia or physical impairment. Of these, 380 reported physician-diagnosed fibromyalgia 11 years later during the study follow-up. Each study phase included a series of physical examinations and measurements and detailed self-reported questionnaires. At follow-up, the study comprised 9,942 normal-weight, 4,245 overweight, and 1,481 obese women.

Women who reported that they exercised four or more times a week were 29% less likely to develop fibromyalgia than were women who described themselves as inactive. Obese women (body mass index of at least 30 kg/m^2) had a 64% higher risk than normal weight women of developing the disorder, even after adjustments for potential confounding factors such as age, smoking, and psychological well-being.

In overweight and obese women (BMI of at least 25 kg/m^2) who initially reported exercising 1 hour a week or more, the relative risk of fibromyalgia was somewhat reduced compared with women in the same BMI group who were inactive (relative risk, 1.72 vs. 2.09), suggesting a benefit of exercise in preventing fibromyalgia independent of BMI.

The authors said the study was limited because information about exercise habits was self-reported and not followed up in the second part of the cohort. They acknowledged that "genetic predisposition, sociopsychological factors, adverse life events and occupational exposures (eg., work stress), could be of importance," but had not been included in their analysis. ■