

Data Back Broader Indication for Sodium Oxybate

Trial results lead Xyrem maker to seek approval of drug for narcolepsy symptoms beyond cataplexy.

BY BRUCE JANCIN
Denver Bureau

DENVER — Sodium oxybate (Xyrem) is effective not only for cataplexy—its only approved indication at present—but also for the other primary symptoms of narcolepsy, investigators reported at the annual meeting of the Associated Professional Sleep Societies.

Based on data from two randomized clinical trials presented at the meeting, the drug's manufacturer, Orphan Medical Inc., has submitted a supplemental New Drug Application to the Food and Drug Administration. If approval is granted, sodium oxybate's expanded indication would make it the first drug approved for treatment of all the primary symptoms of narcolepsy: excessive daytime sleepiness; fragmented sleep; and cataplexy, the sudden, brief loss of muscle tone frequently experienced by narcoleptics during periods of emotional intensity such as surprise, laughter, or anger.

Terri E. Weaver, Ph.D., noted that in the last few years, quality of life issues in patients with incurable chronic illnesses have drawn greater regulatory and clinical attention. And the quality of life impact of narcolepsy, she stressed, is profound: In one study, the impact was rated greater than living with Parkinson's disease.

"Individuals with narcolepsy are struggling to complete their activities of daily living," said Dr. Weaver of the University

of Pennsylvania, Philadelphia. She presented the first-ever study of sodium oxybate's quality of life impact in narcoleptic patients. The double-blind, placebo-controlled, 8-week trial involved 228 patients randomized to receive either placebo or 4.5 g, 6 g, or 9 g of sodium oxybate per night in two equally divided doses at bedtime and from 2½ to 4 hours later.

Quality of life was assessed with the Functional Outcomes of Sleep Questionnaire administered at baseline, 4 weeks, and 8 weeks. Patients assigned to 4.5 g/night showed no quality of life gains. But those who received 6 g or 9 g experienced significant improvement in four of the five domains measured by this instrument: general productivity, vigilance, social outcome, and activity level. The only domain in which they didn't fare significantly better than placebo was the intimacy/sexual relationships subscale.

The benefit was greater with the 9-g dose. "The effect size was clinically meaningful and quite large," she noted.

The potential for improved quality of life needs to be presented to patients in the context of the possible treatment disadvantages so they can make an informed decision. Patients on sodium oxybate experience a deep sleep and increased arousal threshold. They may not hear a smoke alarm, a late-night telephone call, or a child's cry. "Individuals who have children at home have to weigh the benefit of having a good night's sleep and being able to

function and take care of those children during the day. We all know daytime sleepiness and some of the other effects of narcolepsy can be hazardous, too, in terms of caring for young ones," Dr. Weaver said.

Jed E. Black, M.D., presented another phase III trial, this one designed to assess the relative efficacy of sodium oxybate when taken as monotherapy or with modafinil (Provigil), a widely used wakefulness-promoting agent approved for treatment of the excessive daytime sleepiness component of narcolepsy. The double-blind, 230-patient trial began with all participants on 200-600 mg/day of modafinil. They were then randomized to receive modafinil plus placebo, modafinil plus sodium oxybate, placebo plus sodium oxybate, or double placebos. The sodium oxybate dose was 6 g/night for the first 4 weeks and 9 g thereafter.

Monotherapy with sodium oxybate or modafinil appeared to be equally effective in terms of the primary study end point,

reduction in excessive daytime sleepiness as measured by the Maintenance of Wakefulness Test, the Epworth Sleepiness Scale, and patient self-report. The improvement was greater with the 9-g dose of sodium oxybate than with the 6-g dose. But combination therapy was most effective of all, not only in terms of reduced daytime sleepiness but also consolidation of fragmented sleep and enhanced slow-wave sleep, said Dr. Black of Stanford (Calif.) University. Side effects that occurred more often with sodium oxybate than placebo in the trials included nausea, dizziness,

headache, sleepiness, and bedwetting.

Prior to its 2002 approval as a tightly controlled schedule-III drug for cataplexy, sodium oxybate was available as γ -hydroxybutyrate in health food stores. During that era it was abused as a recreational drug and implicated as a "date rape" drug.

Both randomized trials were sponsored by Orphan Medical. Dr. Weaver serves as a consultant to the company. ■



One study rated narcolepsy's impact as greater than living with Parkinson's disease.

DR. WEAVER

FDA Clears Keppra for Use in Pediatric Partial-Onset Seizure

BY DAMIAN McNAMARA
Miami Bureau

The Food and Drug Administration approved a new pediatric indication for an antiepileptic drug as adjunctive treatment of partial-onset seizures in patients 4 years of age and older.

Levetiracetam (Keppra, UCB Pharma Inc.) effectively reduced seizure frequency in this population, judging from findings from a double-blind, multicenter study. The FDA considered data from the study during its priority review for the new indication.

Investigators randomized 101 patients to levetiracetam and 97 to placebo. Children taking levetiracetam for 14 weeks experienced a 27% reduction in weekly partial seizure frequency, compared with no reduction in children taking placebo. All participants were 4-16 years old, with refractory partial-onset seizures.

The initial daily dose for pediatric patients 4-15 years old is 20 mg/kg, given as twice-daily dosing (10 mg/kg b.i.d.). Increase the daily dose every 2 weeks by 20-mg/kg increments to the recommended daily dose of 60 mg/kg (30 mg/kg b.i.d.). If a patient cannot tolerate a daily dose of

60 mg/kg, the daily dose may be reduced, according to the package insert.

Although other agents are approved for pediatric seizure control, the levetiracetam study is the first to include only treatment-resistant seizures, according to Tracy A. Glauser, M.D., lead author of the study (in press). He added that about 30% of children do not achieve adequate seizure control with existing drugs, which include oxcarbazepine (Trileptal), lamotrigine (Lamictal), gabapentin (Neurontin), and topiramate (Topamax).

Partial-onset seizures account for approximately two-thirds of epilepsy among 4- to 16-year-old children.

FDA approval "allows neurologists and pediatricians who treat children with partial seizures to know it is efficacious and well tolerated. It validates its use in children," said Dr. Glauser, of Cincinnati Children's Hospital Medical Center.

Somnolence, fatigue, and behavioral abnormalities (including agitation, anxiety, and apathy) were associated with levetiracetam use in the study.

Keppra has been approved for use in U.S. adults since 1999. Dr. Glauser is a consultant for UCB Pharma. ■

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