After ENHANCE, Next Steps on Vytorin Weighed

BY ALICIA AULT
Associate Editor, Practice Trends

The Food and Drug Administration said that it is considering, but has not yet determined, whether data from the ENHANCE study of Vytorin warrants any regulatory action.

The agency posted an "early communication" and a MedWatch safety report on its Web site alerting the public and health care practitioners that it is aware of the data but that it has not yet fully examined what appear to be equivocal results.

In a press briefing, Dr. John Jenkins, director of the FDA's Office of New Drugs, said the agency hopes to determine why the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial results were equivocal, with the combination not affecting plaque size in carotid arteries.

Agency officials who participated in the briefing said they were scratching their heads over the results, given that both ezetimibe and simvastatin have been shown to lower LDL cholesterol levels in ENHANCE and in other studies. LDL is a validated surrogate end point, they said.

FDA reviewers will evaluate the data with an eye on potential safety issues, Dr. Jenkins said. "We don't see any reason to change the label or the approved indications based on this study," he said.

He said it may take several months for the agency to receive the data from Merck & Co. and Schering-Plough Pharmaceuticals, the companies that conducted the ENHANCE study, and up to 6 months after that to complete the review.

A press release revealing the equivocal results issued by Merck and Schering-Plough set off a firestorm of criticism. The House Energy and Commerce Committee and the Senate Finance Committee are investigating the timing of the data release

and myriad other issues around Vytorin. It also prompted a torrent of class action suits alleging marketing fraud by the two drug makers.

The agency said physicians should not stop prescribing Vytorin or Zetia (ezetimibe), but should, in conjunction with patients, "carefully consider the available data and current labeling for Zetia and Vytorin as they make individual treatment decisions."

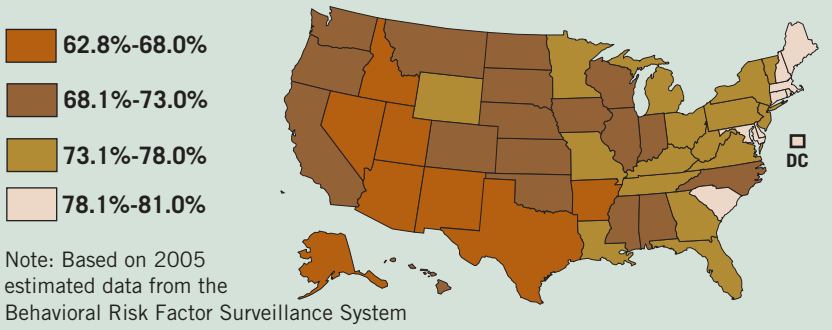
Dr. Jenkins pointed out that neither of these products has any data on reduction of heart attack or stroke as of yet. Cardiovascular events will be measured in the companies' ongoing Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), which will be completed in 2011.

"If a physician wants the certainty of using a product that has outcomes data, [there are] a large number of those products available," he said.

Merck and Schering-Plough "acted with integrity and good faith in connection with the trial," said Thomas Koestler, Ph.D., president of the Schering-Plough Research Institute. "We stand behind Vytorin and Zetia and stand behind our science," said Peter S. Kim, Ph.D., Merck Research Laboratories president. ■

DATA WATCH

Percentage of Adults Who Had Cholesterol Checked Is Highest on the East Coast



Note: Based on 2005 estimated data from the Behavioral Risk Factor Surveillance System on the percentage of adults who had their cholesterol checked during the preceding 5 years.
Source: Centers for Disease Control and Prevention

Elsevier Global Medical News

[†] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[‡] Investigator term; summary level term is amblyopia.

Controlled Studies in Postherpetic Neuralgia *Adverse Reactions Leading to Discontinuation* In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with LYRICA and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the LYRICA group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each). *Most Common Adverse Reactions* Table 2 lists all adverse reactions, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined LYRICA group for which the incidence was greater in this combined LYRICA group than in the placebo group. In addition, an event is included, even if the incidence in the all LYRICA group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 2 Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body System - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal[†]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision[‡]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye disorder	0	1	1	2	1	0
Urogenital system						
Urinary incontinence	0	1	1	2	1	0
Digestive system						
Increased appetite	2	3	6	5	1	
Dry mouth	1	2	6	4	1	
Constipation	1	1	7	4	2	
Metabolic and nutritional disorders						
Weight gain	5	7	16	12	1	
Peripheral edema	3	3	6	5	2	
Nervous system						
Dizziness	18	31	38	32	11	
Somnolence	11	18	28	22	11	
Ataxia	6	10	20	15	4	
Tremor	3	7	11	8	4	
Thinking abnormal[‡]	4	8	9	8	2	
Amnesia	3	2	6	5	2	
Speech disorder	1	2	7	5	1	
Incoordination	1	3	6	4	1	
Abnormal gait	1	3	5	4	0	
Twitching	0	4	5	4	1	
Confusion	1	2	5	4	2	
Myoclonus	1	0	4	2	0	
Special senses						
Blurred vision[§]	5	8	12	10	4	
Diplopia	5	7	12	9	4	
Abnormal vision	3	1	5	4	1	

* PGB: pregabalin
[†] Excludes patients who received the 50 mg dose in Study E1 (included in full prescribing information).
[‡] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[§] Investigator term; summary level term is amblyopia.

Controlled Add-On Studies in Adjunctive Therapy for Adult Patients with Partial Onset Seizures *Adverse Reactions Leading to Discontinuation* Approximately 15% of patients receiving LYRICA and 6% of patients receiving placebo in add-on epilepsy trials discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients in the placebo group withdrew due to each of these events. Other adverse reactions that led to discontinuation of at least 1% of patients in the LYRICA group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients). *Most Common Adverse Reactions* Table 3 lists all dose-related adverse reactions occurring in at least 2% of all LYRICA-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received LYRICA and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1 to 3 other AEDs, it is not possible to determine whether the following adverse reactions can be ascribed to LYRICA alone, or the combination of LYRICA and other AEDs. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 3 Dose-related treatment-emergent adverse reaction incidence in controlled trials in adjunctive therapy for adult patients with partial onset seizures (Events in at least 2% of all LYRICA-treated patients and the adverse reaction in the 600 mg/day group was ≥2% the rate in both the placebo and 150 mg/day groups)

Body System - Preferred term	150 mg/d [N=185] %	300 mg/d [N=90] %	600 mg/d [N=395] %	All PGB* [N=670][†] %	Placebo [N=294] %
Body as a whole					
Accidental injury	7	11	10	9	5
Pain	3	2	5	4	3

* PGB: pregabalin
[†] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[‡] Investigator term; summary level term is amblyopia.

Controlled Studies with Fibromyalgia *Adverse Reactions Leading to Discontinuation* In clinical trials of patients with fibromyalgia, 19% of patients treated with pregabalin (150–600 mg/day) and 10% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (6%) and somnolence (3%). In comparison, <1% of placebo-treated patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue, headache, balance disorder, and weight increased. Each of these adverse reactions led to withdrawal in approximately 1% of patients. *Most Common Adverse Reactions* Table 4 lists all adverse reactions, regardless of causality, occurring in ≥2% of patients with fibromyalgia in the 'all pregabalin' treatment group for which the incidence was greater than in the placebo treatment group. A majority of pregabalin-treated patients in clinical studies experienced adverse reactions with a maximum intensity of "mild" or "moderate".

Table 4 Treatment-emergent adverse reaction incidence in controlled trials in Fibromyalgia (Events in at least 2% of all LYRICA-treated patients and occurring more frequently in the all pregabalin-group than in the placebo treatment group)

System Organ Class - Preferred term	150 mg/d [N=132] %	300 mg/d [N=502] %	450 mg/d [N=505] %	600 mg/d [N=378] %	All PGB* [N=1517] %	Placebo [N=505] %
Ear and Labyrinth Disorders						
Vertigo	2	2	2	1	2	0
Eye Disorders						
Vision blurred	8	7	7	12	8	1
Gastrointestinal Disorders						
Dry mouth	7	6	9	9	8	2
Constipation	4	4	7	10	7	2
Vomiting	2	3	3	2	3	2
Flatulence	1	1	2	2	2	1
Abdominal distension	2	2	2	2	2	1
General Disorders and Administrative Site Conditions						
Fatigue	5	7	6	8	7	4
Edema peripheral	5	5	6	9	6	2
Chest pain	2	1	1	2	2	1
Feeling abnormal	1	3	2	2	2	0
Edema	1	2	1	2	2	1
Feeling drunk	1	2	1	2	2	0
Infections and Infestations						
Sinusitis	4	5	7	5	5	4
Investigations						
Weight increased	8	10	10	14	11	2
Metabolism and Nutrition Disorders						
Increased appetite	4	3	5	7	5	1
Fluid retention	2	3	3	2	2	1
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	4	3	3	6	4	2
Muscle spasms	2	4	4	4	4	2
Back pain	2	3	4	3	3	3
Nervous System Disorders						
Dizziness	23	31	43	45	38	9
Somnolence	13	18	22	22	20	4
Headache	11	12	14	10	12	12
Disturbance in attention	4	4	6	6	5	1
Balance disorder	2	3	6	9	5	0
Memory impairment	1	3	4	4	3	0
Coordination abnormal	2	1	2	2	2	1
Hypoaesthesia	2	2	3	2	2	1
Lethargy	2	2	1	2	2	0
Tremor	0	1	3	2	2	0
Psychiatric Disorders						
Euphoric Mood	2	5	6	7	6	1
Confusional state	0	2	3	4	3	0
Anxiety	2	2	2	2	2	1
Disorientation	1	0	2	1	2	0