

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

LYRICA® (PREGABALIN) CAPSULES®

BRIEF SUMMARY: For full prescribing information, see package insert.

INDICATIONS AND USAGE

LYRICA is indicated for:

- Management of neuropathic pain associated with diabetic peripheral neuropathy
- Management of postherpetic neuralgia
- Adjunctive therapy for adult patients with partial onset seizures
- Management of fibromyalgia

CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS AND PRECAUTIONS

Angioedema There have been postmarketing reports of angioedema in patients during initial and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. LYRICA should be discontinued immediately in patients with these symptoms. Caution should be exercised when prescribing LYRICA to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema. **Hypersensitivity** There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with LYRICA. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. LYRICA should be discontinued immediately in patients with these symptoms. **Withdrawal of Antiepileptic Drugs (AEDs)** As with all AEDs, LYRICA should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If LYRICA is discontinued this should be done gradually over a minimum of 1 week. **Peripheral Edema** LYRICA treatment may cause peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. In controlled clinical trials the incidence of peripheral edema was 6% in the LYRICA group compared with 2% in the placebo group. In controlled clinical trials, 0.5% of LYRICA patients and 0.2% placebo patients withdrew due to peripheral edema. Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with LYRICA only, and 19% (23/120) of patients who were on both LYRICA and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on LYRICA only; and 7.5% (9/120) of patients on both drugs. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents. Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients. **Dizziness and Somnolence** LYRICA may cause dizziness and somnolence. Patients should be informed that LYRICA-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery [see Patient Counseling Information]. In the LYRICA controlled trials, dizziness was experienced by 31% of LYRICA-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of LYRICA-treated patients compared to 7% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of LYRICA therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal (4% each) from controlled studies. In LYRICA-treated patients reporting these adverse reactions in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients. **Weight Gain** LYRICA treatment may cause weight gain. In LYRICA controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of LYRICA-treated patients and 2% of placebo-treated patients. Few patients treated with LYRICA (0.3%) withdrew from controlled trials due to weight gain. LYRICA associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema [see Warnings and Precautions]. Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of LYRICA-associated weight gain are unknown. Among diabetic patients, LYRICA-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received LYRICA for at least 2 years, the average weight gain was 5.2 kg. While the effects of LYRICA-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, LYRICA treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1c}). **Abrupt or Rapid Discontinuation** Following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. LYRICA should be tapered gradually over a minimum of 1 week rather than discontinued abruptly. **Tumorigenic Potential** In standard preclinical *in vivo* lifetime carcinogenicity studies of LYRICA, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during LYRICA's premarketing development provides no direct means to assess its potential for inducing tumors in humans. In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening pre-existing tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment. **Ophthalmological Effects** In controlled studies, a higher proportion of patients treated with LYRICA reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued LYRICA treatment due to vision-related events (primarily blurred vision). Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with LYRICA, and 5% of placebo-treated patients. Visual field changes were detected in 13% of LYRICA-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of LYRICA-treated and 2% of placebo-treated patients. Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions [see Patient Counseling Information]. **Creatine Kinase Elevations** LYRICA treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for LYRICA-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 1.5% of patients on LYRICA and 0.7% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three LYRICA-treated subjects had

events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and LYRICA is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. LYRICA treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur. **Decreased Platelet Count** LYRICA treatment was associated with a decrease in platelet count. LYRICA-treated subjects experienced a mean maximal decrease in platelet count of $20 \times 10^3/\mu\text{L}$, compared to $11 \times 10^3/\mu\text{L}$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of LYRICA patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and $<150 \times 10^3/\mu\text{L}$. A single LYRICA treated subject developed severe thrombocytopenia with a platelet count less than $20 \times 10^3/\mu\text{L}$. In randomized controlled trials, LYRICA was not associated with an increase in bleeding-related adverse reactions. **PR Interval Prolongation** LYRICA treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at LYRICA doses ≥ 300 mg/day. This mean change difference was not associated with an increased risk of PR increase $\geq 25\%$ from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse reactions of second or third degree AV block. Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In all controlled and uncontrolled trials across various patient populations during the premarketing development of LYRICA, more than 10,000 patients have received LYRICA. Approximately 5000 patients were treated for 6 months or more, over 3100 patients were treated for 1 year or longer, and over 1400 patients were treated for at least 2 years. **Adverse Reactions Most Commonly Leading to Discontinuation in All Premarketing Controlled Clinical Studies** In premarketing controlled trials of all populations combined, 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 adverse reactions most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse reactions that led to discontinuation from controlled trials more frequently in the LYRICA group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each). **Most Common Adverse Reactions in All Premarketing Controlled Clinical Studies** In premarketing controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with LYRICA than by subjects treated with placebo ($\geq 5\%$ and twice the rate of that seen in placebo). **Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy Adverse Reactions Leading to Discontinuation** In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with LYRICA and 4% 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 (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the LYRICA group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients. **Most Common Adverse Reactions** Table 1 lists all adverse reactions, regardless of causality, occurring in $\geq 1\%$ of patients with neuropathic pain associated with diabetic neuropathy in the combined LYRICA group for which the incidence was greater in this combined LYRICA group than 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 1 Treatment-emergent adverse reaction incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all LYRICA than in the placebo group)

Body System - Preferred term	75 mg/d [N=77] %	150 mg/d [N=212] %	300 mg/d [N=321] %	600 mg/d [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Body as a whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive system						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal [†]	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory system						
Dyspnea	3	0	2	2	2	1
Special senses						
Blurry vision [‡]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

*PGB: pregabalin

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

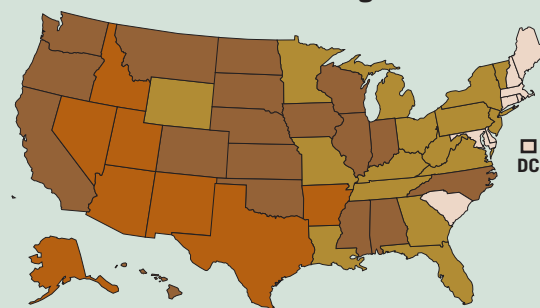
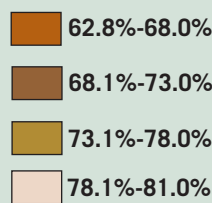
Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), which will be completed in 2011.

“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

* 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

* 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 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

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 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