

# FDA Flags Liver Damage Risks With Diclofenac

BY ELIZABETH MEHCATIE

Warnings about the potential risk of hepatotoxicity associated with the use of diclofenac have been added to the labels of all products containing the nonsteroidal anti-inflammatory drug, the Food and Drug Administration announced.

A notice on the FDA's MedWatch site said that the manufacturers—Endo Phar-

maceuticals Inc. and Novartis Consumer Health Inc.—had revised the “hepatic effects” section of the diclofenac topical gel label to include new warnings and precautions about the potential for elevated liver function tests during treatment with diclofenac products, including the formulation marketed as Voltaren Gel 1%.

There have been postmarketing reports of severe hepatic reactions including liver necrosis, jaundice, fulminant

hepatitis with and without jaundice, and liver failure in patients treated with diclofenac, according to the FDA. Some cases have been fatal or have resulted in liver transplantation.

Because severe hepatotoxicity may be asymptomatic, the FDA and the revised label both recommend that clinicians periodically measure transaminase levels in patients taking diclofenac long term. Levels should be monitored within 4-8

weeks after initiating treatment, according to the FDA notice.

The labeling changes are summarized in a Dear Health Care Professional letter issued by the manufacturers. ■

For more information, call 800-452-0051. The MedWatch notice and letter can be viewed at [www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm193047.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm193047.htm).

## LYRICA® (pregabalin) CAPSULES ©

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

### INDICATIONS AND USAGE

LYRICA is indicated for:

- Management of fibromyalgia

### DOSE AND ADMINISTRATION

LYRICA is given orally with or without food. When discontinuing LYRICA, taper gradually over a minimum of 1 week.

### Fibromyalgia:

- Administer in 2 divided doses per day
- Begin dosing at 150 mg/day
- May be increased to 300 mg/day within 1 week
- Maximum dose of 450 mg/day
- Dose should be adjusted for patients with reduced renal function

### CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its other 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. **Suicidal Behavior and Ideation** Antiepileptic drugs (AEDs), including LYRICA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing LYRICA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers. **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 gain 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 thiazolidinedione 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. 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<sub>1c</sub>). **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 [see *Nonclinical Toxicology*]. The clinical significance of this finding is unknown. Clinical experience during LYRICA 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. **Ophthalmologic 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 fundoscopic 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. Fundoscopic 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. **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 x 10<sup>9</sup>/L, compared to 11 x 10<sup>9</sup>/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 x 10<sup>9</sup>/L. A single LYRICA treated subject developed severe thrombocytopenia with a platelet count less than 20 x 10<sup>9</sup>/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 ≥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 (≥5% and twice the rate of that seen in placebo).

*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 2 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 2 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] %
<b>Ear and Labyrinth Disorders</b>						
Vertigo	2	2	2	1	2	0
<b>Eye Disorders</b>						
Vision blurred	8	7	7	12	8	1
<b>Gastrointestinal Disorders</b>						
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
<b>General Disorders and Administrative Site Conditions</b>						
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
<b>Infections and Infestations</b>						
Sinusitis	4	5	7	5	5	4
<b>Investigations</b>						
Weight increased	8	10	10	14	11	2
<b>Metabolism and Nutrition Disorders</b>						
Increased appetite	4	3	5	7	5	1
Fluid retention	2	3	3	2	2	1
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Arthralgia	4	3	3	6	4	2
Muscle spasms	2	4	4	4	4	2
Back pain	2	3	4	3	3	3
<b>Nervous System Disorders</b>						
Dizziness	23	31	43	45	38	9
Somnolence	13	18	22	22	20	4
Headache	1	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
Hypoesthesia	2	2	3	2	2	1
Lethargy	2	2	1	2	2	0
Tremor	0	1	3	2	2	0
<b>Psychiatric Disorders</b>						
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
Depression	2	2	2	2	2	2
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Pharyngolaryngeal pain	2	1	3	3	2	2

\*PGB: pregabalin

*Other Adverse Reactions Observed During the Clinical Studies of LYRICA* Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse reactions are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the *Warnings and Precautions* section. Body as a Whole - *Frequent*: Abdominal pain, Allergic reaction, Fever; *Infrequent*: Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction; *Rare*: Anaphylactoid reaction, Ascites, Granuloma, Hangover