Figure 6: Responder rate by add-on epilepsy study

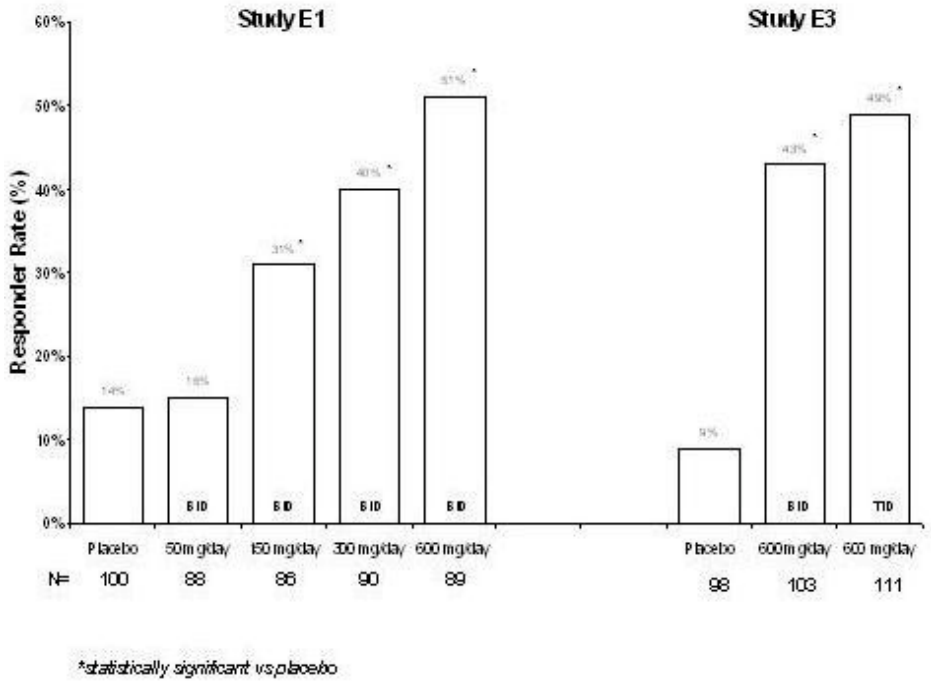
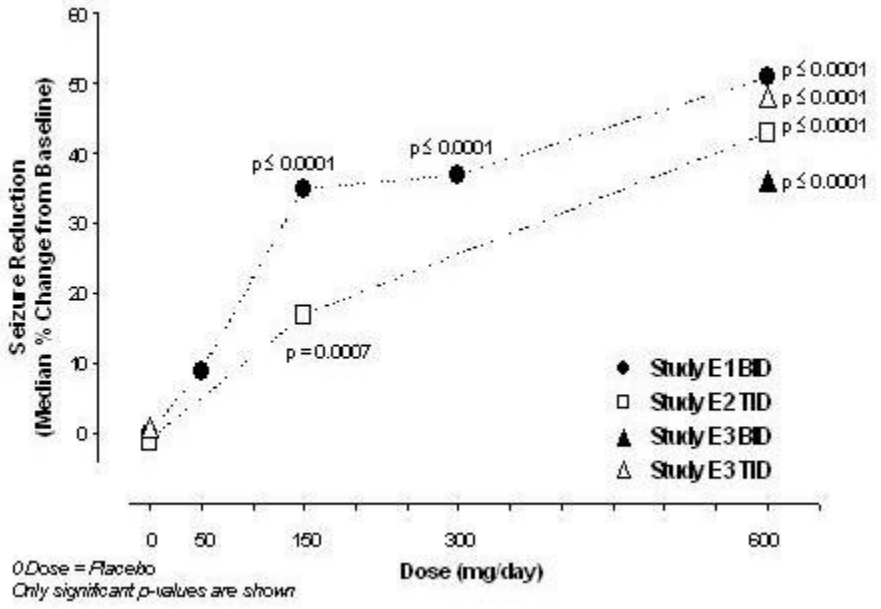


Figure 7: Seizure Reduction by Dose (All Partial Onset Seizures) for Studies E1, E2, and E3



Subset evaluations of the antiseizure efficacy of LYRICA showed no clinically important differences as a function of age, gender, or race.

Adjunctive Therapy for Partial Onset Seizures in Pediatric Patients 4 to Less Than 17 Years of Age

The efficacy of LYRICA as adjunctive therapy in partial onset seizures was established in a 12-week, randomized, double-blind, placebo-controlled, multicenter study in pediatric patients 4 years to less than 17 years of age with partial onset seizures with or without secondary generalization. During an 8-week baseline period, patients had to experience at least 6 partial onset seizures with no seizure-free period exceeding 4 weeks. The mean duration of epilepsy was 6 years and the mean and median baseline seizure frequencies were 57 and 18 seizures per month, respectively. Approximately 74% of the patients were taking 2 to 3 concurrent AEDs at baseline. Among the LYRICA-treated patients, 87% completed the double-blind phase of the study.

In this study, LYRICA 2.5 mg/kg/day (maximum 150 mg/day) and 10 mg/kg/day (maximum 600 mg/day) were compared to placebo. Administration of each daily dose was divided into two equal doses (twice a day dosing). Because of higher weight-normalized clearance in patients with body weight less than 30 kg *[see Clinical Pharmacology (12.3)]*, the LYRICA dose was increased by 40% to 3.5 mg/kg/day for patients weighing less than 30 kg randomized to the 2.5 mg/kg/day group or to 14 mg/kg/day for patients randomized to the 10 mg/kg/day group.

Table 11 shows median baseline seizure rates, median percent change from baseline in seizure rates, and percent difference relative to placebo (derived from the primary analysis model) by dose.

Table 11. Seizure Response in Controlled Add-On Partial Onset Seizure Study in Pediatric Patients 4 to Less Than 17 Years of Age

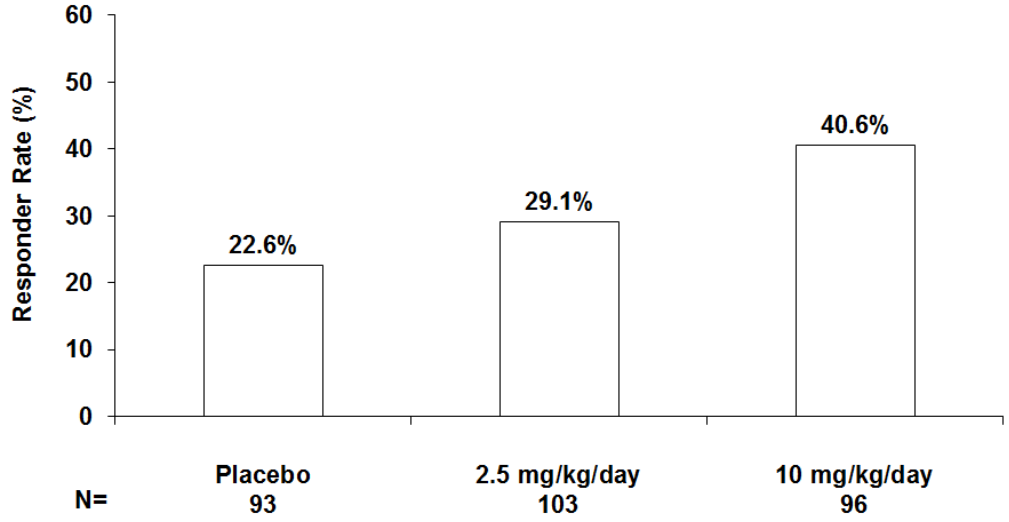
Daily Dose of LYRICA	N	Median Baseline Seizure Frequency/ 28 days	Median % Change from Baseline	% Difference Relative to Placebo	p-value, versus placebo
Placebo	93	16.5	-16.9	Not applicable	
2.5 mg/kg/day (BID)[a]	104	23.8	-27.3	-10.5	0.2577
10 mg/kg/day (BID)[b]	97	17.5	-37.1	-21.0	0.0185

Abbreviations: BID=twice daily; N=number.
a. 2.5 mg/kg/day: Maximum dose 150 mg/day. Includes patients less than 30 kg for whom dose was adjusted to 3.5 mg/kg/day.
b. 10 mg/kg/day: Maximum dose 600 mg/day. Includes patients less than 30 kg for whom dose was adjusted to 14 mg/kg/day.

There was evidence of a dose-response relationship for total daily doses of LYRICA between 2.5 mg/kg/day and 10 mg/kg/day. A significant improvement in seizure rate was observed for LYRICA 10 mg/kg/day group compared with placebo. While the 2.5 mg/kg/day group performed numerically better than placebo, this difference was not statistically significant.

A key secondary efficacy measure, the responder rate (proportion of patients with greater than or equal to 50% reduction from baseline in partial seizure frequency) showed improvements for LYRICA groups compared with placebo. The following figure displays responder rate by dose:

Figure 8: Responder Rate (Greater than or Equal to 50% Reduction)



14.4 Management of Fibromyalgia

The efficacy of LYRICA for management of fibromyalgia was established in one 14-week, double-blind, placebo-controlled, multicenter study (F1) and one six-month, randomized withdrawal study (F2). Studies F1 and F2 enrolled patients with a diagnosis of fibromyalgia using the American College of Rheumatology (ACR) criteria (history of widespread pain for 3 months, and pain present at 11 or more of the 18 specific tender point sites). The studies showed a reduction in pain by visual analog scale. In addition, improvement was demonstrated based on a patient global assessment (PGIC), and on the Fibromyalgia Impact Questionnaire (FIQ).

Study F1: This 14-week study compared LYRICA total daily doses of 300 mg, 450 mg and 600 mg with placebo. Patients were enrolled with a minimum mean baseline pain score of greater than or equal to 4 on an 11-point numeric pain rating scale and a score of greater than or equal to 40 mm on the 100 mm pain visual analog scale (VAS). The baseline mean pain score in this trial was 6.7. Responders to placebo in an initial one-week run-in phase were not randomized into subsequent phases of the study. A total of 64% of patients randomized to LYRICA completed the study. There was no evidence of a greater effect on pain scores of the 600 mg daily dose than the 450 mg daily dose, but there was evidence of dose-dependent adverse reactions [*see Adverse Reactions (6.1)*]. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study. The results are summarized in Figure 9 and Table 12.

For various levels of improvement in pain intensity from baseline to study endpoint, Figure 9 shows the fraction of patients achieving that level of improvement. The figure is cumulative. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 9: Patients Achieving Various Levels of Improvement in Pain Intensity – Fibromyalgia Study F1

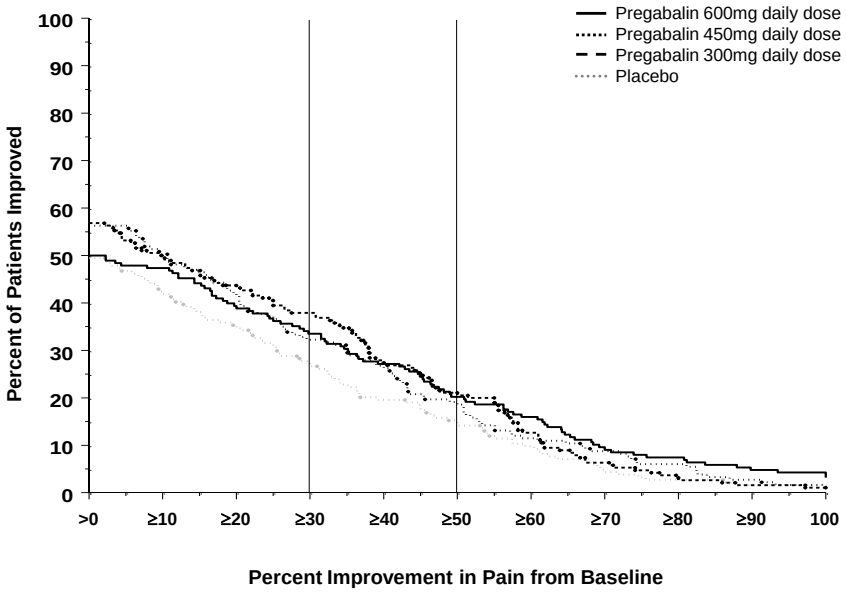


Table 12. Patient Global Response in Fibromyalgia Study F1

Patient Global Impression of Change		
Treatment Group (mg/day)	**% Any Improvement**	**95% CI**
Placebo	47.6	(40.0,55.2)
PGB 300	68.1	(60.9, 75.3)
PGB 450	77.8	(71.5, 84.0)
PGB 600	66.1	(59.1, 73.1)

PGB = Pregabalin

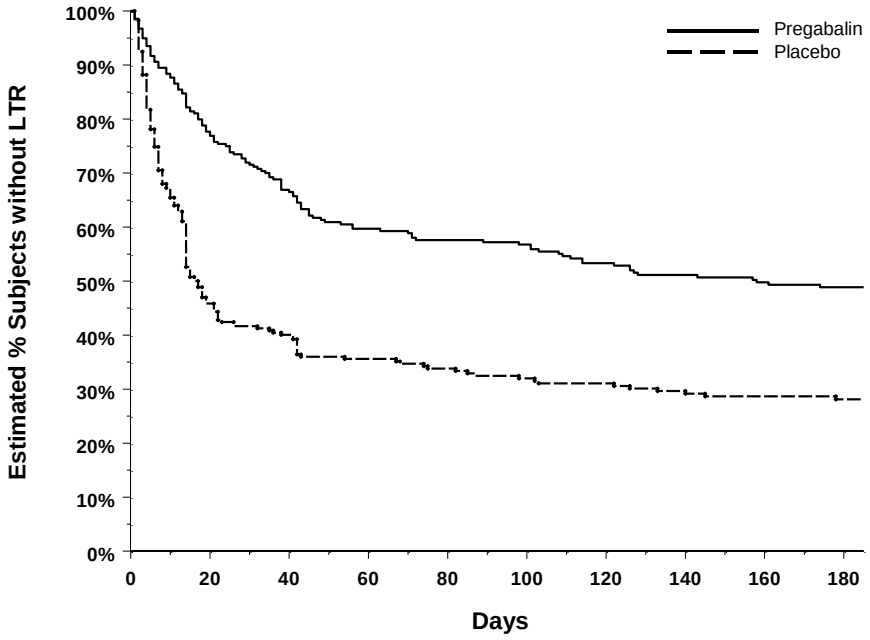
Study F2: This randomized withdrawal study compared LYRICA with placebo. Patients were titrated during a 6-week open-label dose optimization phase to a total daily dose of 300 mg, 450 mg, or 600 mg. Patients were considered to be responders if they had both: 1) at least a 50% reduction in pain (VAS) and, 2) rated their overall improvement on the PGIC as "much improved" or "very much improved." Those who responded to treatment were then randomized in the double-blind treatment phase to either the dose achieved in the open-label phase or to placebo. Patients were treated for up to 6 months following randomization. Efficacy was assessed by time to loss of therapeutic response, defined as 1) less than 30% reduction in pain (VAS) from open-label baseline during two consecutive visits of the double-blind phase, or 2) worsening of FM symptoms necessitating an alternative treatment. Fifty-four percent of patients were able to titrate to an effective and tolerable dose of LYRICA during the 6-week open-label

phase. Of the patients entering the randomized treatment phase assigned to remain on LYRICA, 38% of patients completed 26 weeks of treatment versus 19% of placebo-treated patients.

When considering return of pain or withdrawal due to adverse events as loss of response (LTR), treatment with LYRICA resulted in a longer time to loss of therapeutic response than treatment with placebo. Fifty-three percent of the pregabalin-treated subjects compared to 33% of placebo patients remained on study drug and maintained a therapeutic response to Week 26 of the study. Treatment with LYRICA also resulted in a longer time to loss of response based on the FIQ[1], and longer time to loss of overall assessment of patient status, as measured by the PGIC[2].

[1] Time to worsening of the FIQ was defined as the time to a 1-point increase from double-blind baseline in each of the subscales, and a 5-point increase from double-blind baseline evaluation for the FIQ total score.
[2] Time to PGIC lack of improvement was defined as time to PGIC assessments indicating less improvement than "much improvement."

Figure 10: Time to Loss of Therapeutic Response, Fibromyalgia Study F2 (Kaplan-Meier Analysis)



14.5 Management of Neuropathic Pain Associated with Spinal Cord Injury

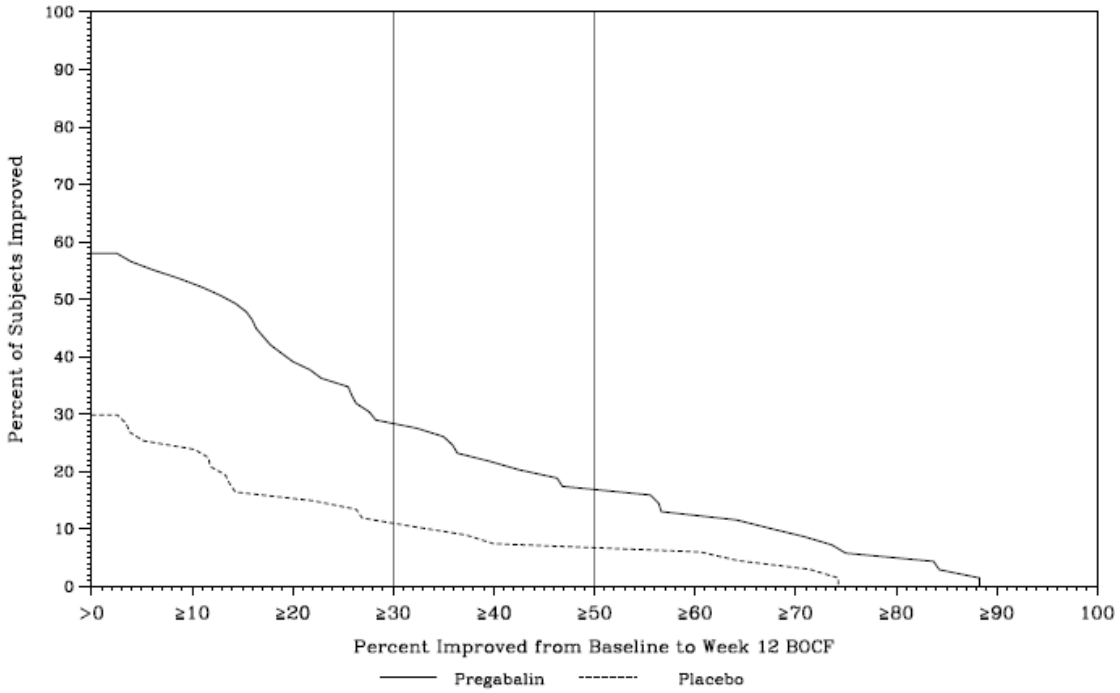
The efficacy of LYRICA for the management of neuropathic pain associated with spinal cord injury was established in two double-blind, placebo-controlled, multicenter studies. Patients were enrolled with neuropathic pain associated with spinal cord injury that persisted continuously for at least three months or with relapses and remissions for at least six months. A total of 63% of patients completed study 1 and 84% completed study 2. The patients had a minimum mean baseline pain score of greater than or equal to 4 on an 11-point numerical pain rating scale

ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.5 to 6.7.

Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if the dose was stable for 30 days prior to screening. Patients were allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the studies.

Study SCI 1: This 12-week, randomized, double-blind, parallel-group, multicenter, flexible dose (150-600 mg/day) study compared pregabalin with placebo. The 12-week study consisted of a 3-week dose adjustment phase and a 9-week dose maintenance phase. Treatment with LYRICA 150-600 mg/day statistically significantly improved the endpoint weekly mean pain score, and increased the proportion of patients with at least a 30% and 50% reduction in pain score from baseline. The fraction of patients achieving various levels of improvement in pain intensity from baseline to Week 12 is presented in Figure 11. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

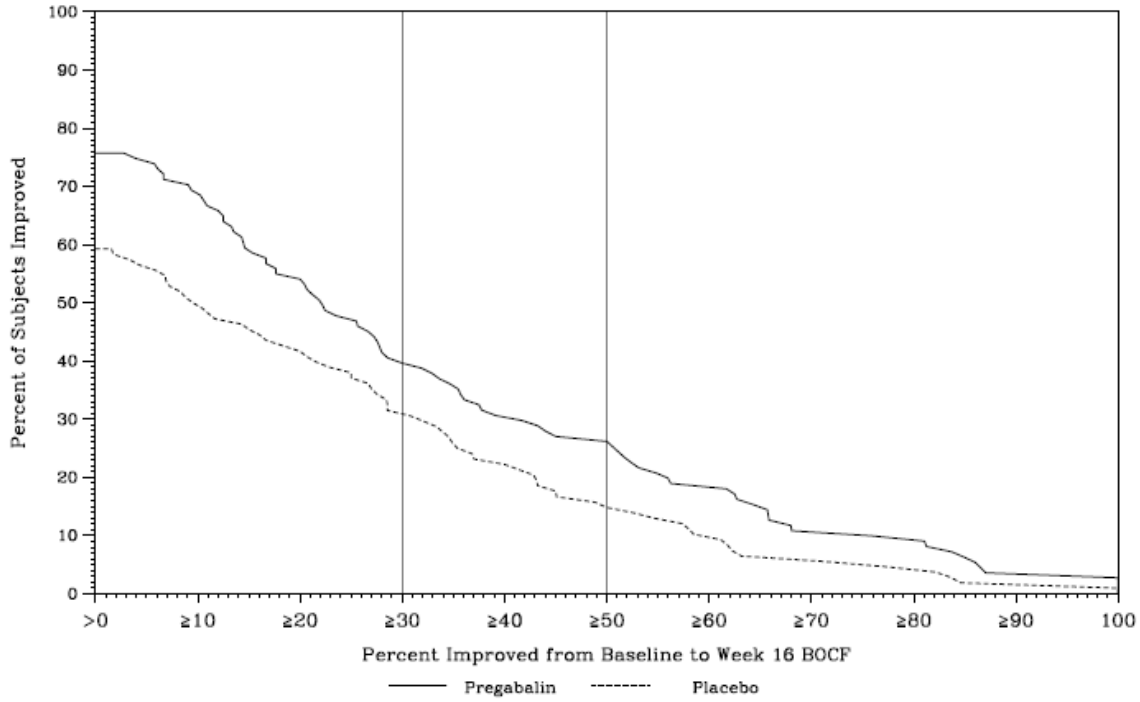
Figure 11: Patients Achieving Various Levels of Improvement in Pain Intensity – Study SCI 1



Study SCI 2: This 16-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, flexible dose (150-600 mg/day, in increments of 150 mg) study compared the efficacy, safety and tolerability of pregabalin with placebo. The 16-week study consisted of a 4-week dose adjustment phase and a 12-week dose maintenance phase. Treatment with LYRICA statistically significantly improved the endpoint weekly mean pain score, and increased the proportion of patients with at least a 30% and 50% reduction in pain score from baseline. The fraction of patients achieving various levels of improvement in pain intensity from baseline to

Week 16 is presented in Figure 12. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 12: Patients Achieving Various Levels of Improvement in Pain Intensity – Study SCI 2



16 HOW SUPPLIED/STORAGE AND HANDLING

25 mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 25" on the body; available in:

Bottles of 90: NDC 0071-1012-68

50 mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 50" and an ink band on the body, available in:

Bottles of 90: NDC 0071-1013-68

Unit-Dose Blister Packages of 100: NDC 0071-1013-41

75 mg capsules:

White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 75" on the body; available in:

Bottles of 90:	NDC 0071-1014-68
Unit-Dose Blister Packages of 100:	NDC 0071-1014-41

100 mg capsules:

Orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 100" on the body, available in:

Bottles of 90:	NDC 0071-1015-68
Unit-Dose Blister Packages of 100:	NDC 0071-1015-41

150 mg capsules:

White hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 150" on the body, available in:

Bottles of 90:	NDC 0071-1016-68
Unit-Dose Blister Packages of 100:	NDC 0071-1016-41

200 mg capsules:

Light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 200" on the body, available in:

Bottles of 90:	NDC 0071-1017-68

225 mg capsules:

White/light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 225" on the body; available in:

Bottles of 90:	NDC 0071-1019-68

300 mg capsules:

White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 300" on the body, available in:

Bottles of 90: NDC 0071-1018-68

20 mg/mL oral solution:

16 fluid ounce white high density polyethylene (HDPE) bottle with a polyethylene-lined closure:

16 fluid ounce bottle NDC 0071-1020-01

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Angioedema

Advise patients that LYRICA may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue LYRICA and immediately seek medical care if they experience these symptoms [*see Warnings and Precautions (5.1)*].

Hypersensitivity

Advise patients that LYRICA has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Instruct patients to discontinue LYRICA and immediately seek medical care if they experience these symptoms *[see Warnings and Precautions (5.2)*].

Adverse Reactions with Abrupt or Rapid Discontinuation

Advise patients to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in increased seizure frequency in patients with seizure disorders, and insomnia, nausea, headache, anxiety, hyperhidrosis, or diarrhea *[see Warnings and Precautions (5.3)]*.

Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including LYRICA, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or

Who should not take LYRICA?

Do not take LYRICA if you are allergic to pregabalin or any of the ingredients in LYRICA.

See **"What is the most important information I should know about LYRICA?"** for the signs of an allergic reaction.

See the end of this leaflet for a complete list of ingredients in LYRICA.

What should I tell my healthcare provider before taking LYRICA?

Before taking LYRICA, tell your healthcare provider about all your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior.
- have kidney problems or get kidney dialysis.
- have heart problems including heart failure.
- have a bleeding problem or a low blood platelet count.
- have abused prescription medicines, street drugs, or alcohol in the past.
- have ever had swelling of your face, mouth, tongue, lips, gums, neck, or throat (angioedema).
- plan to father a child. Animal studies have shown that pregabalin, the active ingredient in LYRICA, made male animals less fertile and caused sperm to change. Also, in animal studies, birth defects were seen in the offspring (babies) of male animals treated with pregabalin. It is not known if these problems can happen in people who take LYRICA.
- **are pregnant or plan to become pregnant. LYRICA may harm your unborn baby.** You and your healthcare provider will decide if you should take LYRICA while you are pregnant.
  - If you become pregnant while taking LYRICA, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy. Information about the registry can also be found at the website, http://www.aedpregnancyregistry.org/.
- **are breastfeeding or plan to breastfeed. LYRICA passes into your breast milk. It is not known if Lyrica can harm your baby.** Talk to your healthcare provider about the best way to feed your baby if you take LYRICA. **Breastfeeding is not recommended while taking LYRICA.**

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins or herbal supplements. LYRICA and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take:

- angiotensin converting enzyme (ACE) inhibitors, which are used to treat many conditions, including high blood pressure. You may have a higher chance for swelling and hives if these medicines are taken with LYRICA.
- Avandia (rosiglitazone) or Actos (pioglitazone) for diabetes. You may have a higher chance of weight gain or swelling of your hands or feet if these medicines are taken with LYRICA.
- any narcotic pain medicine (such as oxycodone), tranquilizers or medicines for anxiety (such as lorazepam). You may have a higher chance for dizziness and sleepiness if these medicines are taken with LYRICA.
- any medicines that make you sleepy.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking with your healthcare provider.

How should I take LYRICA?

- Take LYRICA exactly as prescribed. Your healthcare provider will tell you how much LYRICA to take and when to take it.
- LYRICA may be taken with or without food.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- Do not stop taking LYRICA without talking to your healthcare provider. If you stop taking LYRICA suddenly you may have headaches, nausea, diarrhea, trouble sleeping, increased sweating, or you may feel anxious. If you have epilepsy and you stop taking LYRICA suddenly, you may have seizures more often. Talk with your healthcare provider about how to stop LYRICA slowly.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. Do not take two doses at the same time.
- If you take too much LYRICA, call your healthcare provider or poison control center, or go to the nearest emergency room right away.

What should I avoid while taking LYRICA?

- **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects you.**
- **Do not drink alcohol while taking LYRICA.** LYRICA and alcohol can affect each other and increase side effects such as sleepiness and dizziness.