PREGABALIN- pregabalin capsule
Direct Rx

Pregabalin

MEDICATION GUIDE
Pregabalin (pre-GAB-a-lin) Capsules, CV
Read this Medication Guide before you start taking pregabalin and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about pregabalin, ask your healthcare provider or pharmacist.

What is the most important information I should know about pregabalin capsules?

Pregabalin capsules may cause serious side effects including:

serious, even life-threatening, allergic reactions
suicidal thoughts or actions
serious breathing problems
swelling of your hands, legs and feet
dizziness and sleepiness
These serious side effects are described below:

Serious, even life-threatening, allergic reactions.
Stop taking pregabalin capsules and call your healthcare provider right away if you have any of these signs of a serious allergic reaction:
swelling of your face, mouth, lips, gums, tongue, throat or neck
trouble breathing
rash, hives (raised bumps) or blisters
Like other antiepileptic drugs, pregabalin capsules may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
thoughts about suicide or dying
attempts to commit suicide
new or worse depression
new or worse anxiety
feeling agitated or restless
panic attacks
trouble sleeping (insomnia)
new or worse irritability
acting aggressive, being angry, or violent
acting on dangerous impulses
an extreme increase in activity and talking (mania)
other unusual changes in behavior or mood
If you have suicidal thoughts or actions, do not stop pregabalin capsules without first talking to a healthcare provider.

Stopping pregabalin capsules suddenly can cause serious problems.
Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
Keep all follow-up visits with your healthcare provider as scheduled.
Call your healthcare provider between visits as needed, especially if you are worried about symptoms.
Serious breathing problems can occur when pregabalin is taken with other medicines that can cause severe sleepiness or decreased awareness, or when it is taken by someone who already has breathing problems. Watch for increased sleepiness or decreased breathing when starting pregabalin or when the dose is increased. Get help right away if breathing problems occur.
Swelling of your hands, legs and feet. This swelling can be a serious problem for people with heart problems.
Dizziness and sleepiness. Do not drive a car, work with machines, or do other dangerous activities until you know how pregabalin capsules affects you. Ask your healthcare provider about when it will be okay to do these activities.
What is pregablin capsule?

Pregabalin capsule is a prescription medicine used in adults, 18 years of age and older to treat:

pain from damaged nerves (neuropathic pain) that happens with diabetes
pain from damaged nerves (neuropathic pain) that follows healing of shingles
fibromyalgia (pain all over your body)
pain from damaged nerves (neuropathic pain) that follows spinal cord injury
It is not known if pregabalin is safe and effective in people under 18 years of age for the treatment of fibromyalgia and neuropathic pain with diabetes, shingles, or spinal cord injury.

Pregabalin is a prescription medicine used in people 17 years of age and older to treat:

partial onset seizures when taken together with other seizure medicines.
For the treatment of partial onset seizures when taken together with other seizure medicines, it is not known if pregabalin is safe and effective in children under 1 month of age.

Who Should Not Take Pregabalin Capsules?

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

See “What is the most important information I should know about pregabalin capsules?” for the signs of an allergic reaction.

See the end of this Medication Guide for a complete list of ingredients in pregabalin capsules.

What should I tell my healthcare provider before taking pregabalin capsules?

Before taking pregabalin capsules, 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 pregabalin capsules, 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 pregabalin capsules.
are pregnant or plan to become pregnant. Pregabalin capsules may harm your unborn baby.You and your healthcare provider will decide if you should take pregabalin capsules while you are pregnant.
If you become pregnant while taking pregabalin capsules, 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. Pregabalin passes into your breast milk. It is not known if pregabalin can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take pregabalin capsules.
Breastfeeding is not recommended while taking pregabalin capsules.
Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins or herbal supplements. Pregabalin capsules 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 pregabalin capsules.
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 pregabalin capsules.
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 pregabalin capsules.
any opioid pain medicine (such as oxycodone), or medicines for anxiety (such as lorazepam) or insomnia (such as zolpidem). You may have a higher chance for dizziness, sleepiness or serious breathing problems if these medicines are taken with pregabalin capsules.
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 pregabalin capsules?

Take pregabalin capsules exactly as prescribed. Your healthcare provider will tell you how much pregabalin capsules to take and when to take it.
Pregabalin capsules 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 pregabalin capsules without talking to your healthcare provider. If you stop taking pregabalin capsules suddenly you may have headaches, nausea, diarrhea, trouble sleeping, increased sweating, or you may feel anxious. If you have epilepsy and you stop taking pregabalin capsules suddenly, you may have seizures more often. Talk with your healthcare provider about how to stop pregabalin capsules 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 pregabalin capsules, call your healthcare provider or poison control center, or go to the nearest emergency room right away.
What should I avoid while taking pregabalin capsules?

Do not drive a car, work with machines, or do other dangerous activities until you know how pregabalin capsule affects you.
Do not drink alcohol while taking pregabalin capsules. Pregabalin capsules and alcohol can affect each other and increase side effects such as sleepiness and dizziness.
What are the possible side effects of pregabalin capsules?

Pregabalin capsules may cause serious side effects, including:

See “What is the most important information I should know about pregabalin capsules?”
Muscle problems, muscle pain, soreness, or weakness. If you have these symptoms, especially if you feel sick and have a fever, tell your healthcare provider right away.
Problems with your eyesight, including blurry vision. Call your healthcare provider if you have any changes in your eyesight.
Weight gain. If you have diabetes, weight gain may affect the management of your diabetes. Weight gain can also be a serious problem for people with heart problems.
Feeling “high”
The most common side effects of pregabalin capsules in adults are:

dizziness
blurry vision
dry mouth
weight gain
sleepiness
trouble concentrating
swelling of hands and feet
Pregabalin capsules caused skin sores in animal studies. Skin sores did not happen in studies in people. If you have diabetes, you should pay attention to your skin while taking pregabalin capsules and tell your healthcare provider about any sores or skin problems.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of pregabalin capsules. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1800-FDA-1088.

How should I store pregabalin capsules?

Store pregabalin capsules at room temperature, 59°F to 86°F (15°C to 30°C).
Safely throw away any pregabalin capsule that is out of date or no longer needed.
Keep pregabalin capsules and all medicines out of the reach of children.

General information about the safe and effective use of pregabalin capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use pregabalin capsules for a condition for which it was not prescribed. Do not give pregabalin capsules to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about pregabalin capsules that is written for health professionals.

What are the ingredients in pregabalin capsules?

Active ingredient: pregabalin

Inactive ingredients:

pregelatinized starch and talc as inactive ingredients.

Capsule shell: gelatin, titanium dioxide and sodium lauryl sulfate; Orange capsule shell (75 mg, 100 mg, 200 mg, 225 mg and 300 mg strengths): FD&C Blue 1, FD&C Red 40 and FD&C Yellow 6.

Imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

Pediatric use information is approved for Pfizer’s LYRICA (pregabalin) Capsules and Oral Solution products. However, due to Pfizer’s marketing exclusivity rights, this drug product is not labeled with that pediatric information.
Manufactured by:
ScieGen Pharmaceuticals, Inc.
Hauppauge, NY 11788
You can also call 1-855-724-3436.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 1/2021

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

Angioedema

Advise patients that pregabalin 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 pregabalin and immediately seek medical care if they experience these symptoms [see WARNINGS AND PRECAUTIONS (5.1)].

Hypersensitivity

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

Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including pregabalin, 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 behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers [see WARNINGS AND PRECAUTIONS (5.3)].

Respiratory Depression

Inform patients about the risk of respiratory depression. Include information that the risk is greatest for those using concomitant central nervous system (CNS) depressants (such as opioid analgesics) or in those with underlying respiratory impairment. Teach patients how to recognize respiratory depression and advise them to seek medical attention immediately if it occurs [see WARNINGS AND PRECAUTIONS (5.4)].

Dizziness and Somnolence

Counsel patients that pregabalin may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, advise patients not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely [see WARNINGS AND PRECAUTIONS (5.5)].

CNS Depressants

Inform patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines that they may experience additive CNS side effects, such as respiratory depression, somnolence, and dizziness [see WARNINGS AND PRECAUTIONS (5.4, 5.5) and DRUG INTERACTIONS (7)]. Advise patients to avoid consuming alcohol while taking pregabalin, as pregabalin may potentiate the impairment of motor skills and sedating effects of alcohol.

Adverse Reactions with Abrupt or Rapid Discontinuation

Advise patients to take pregabalin 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 (5.6)].

Missed Dose

Counsel patients if they miss a dose, they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at their regularly scheduled time. Instruct patients not to take two doses at the same time.

Weight Gain and Edema

Counsel patients that pregabalin may cause edema and weight gain. Advise patients that concomitant treatment with pregabalin and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure [see WARNINGS AND PRECAUTIONS (5.7, 5.8)].

Ophthalmological Effects

Counsel patients that pregabalin may cause visual disturbances. Inform patients that if changes in vision occur, they should notify their physician [see WARNINGS AND PRECAUTIONS (5.10)].

Creatine Kinase Elevations

Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever [see WARNINGS AND PRECAUTIONS (5.11)].

Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to pregabalin during pregnancy [see USE IN SPECIFIC POPULATIONS (8.1)].

Lactation

Advise nursing mothers that breastfeeding is not recommended during treatment with pregabalin [see USE IN SPECIFIC POPULATIONS (8.2)].

Male Fertility

Inform men being treated with pregabalin who plan to father a child of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain [see NONCLINICAL TOXICOLOGY (13.1) and USE IN SPECIFIC POPULATIONS (8.3)].

Dermatopathy

Instruct diabetic patients to pay particular attention to skin integrity while being treated with pregabalin and to inform their healthcare provider about any sores or skin problems. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with pregabalin was observed in clinical trials [see NONCLINICAL TOXICOLOGY (13.2)].

Manufactured by:
ScieGen Pharmaceuticals, Inc.
Hauppauge, NY 11788
Rev. 1/2021

25 mg capsules:
White to off white powder filled in size “4” hard gelatin capsules with white opaque colored cap and white opaque colored body imprinted “SG” on cap and “350” on body with black ink; available in
Bottles of 30:
Bottles of 90:
Bottles of 1000:
50 mg capsules:
White to off white powder filled in size “3” hard gelatin capsules with white opaque colored cap and white opaque colored body imprinted “SG” on cap and “351” on body with black ink; available in
Bottles of 30:
Bottles of 90:

Bottles of 1000:
75 mg capsules:
White to off white powder filled in size “4” hard gelatin capsules with orange opaque colored cap and white opaque colored body imprinted “SG” on cap and “352” on body with black ink; available in
Bottles of 30:
Bottles of 90:
Bottles of 1000:
100 mg capsules:
White to off white powder filled in size “3” hard gelatin capsules with orange opaque colored cap and orange opaque colored body imprinted “SG” on cap and “353” on body with black ink; available in
Bottles of 30:
Bottles of 90:
Bottles of 1000:
150 mg capsules:
White to off white powder filled in size “2” hard gelatin capsules with white opaque colored cap and white opaque colored body imprinted “SG” on cap and “354” on body with black ink; available in
Bottles of 30:
Bottles of 90:
Bottles of 1000:
200 mg capsules:
White to off white powder filled in size “1” hard gelatin capsules with light orange colored cap and light orange colored body imprinted “SG” on cap and “355” on body with black ink; available in
Bottles of 30:
Bottles of 90:
Bottles of 500:
225 mg capsules:
White to off white powder filled in size “1” hard gelatin capsules with light orange colored cap and white opaque colored body imprinted “SG” on cap and “356” on body with black ink; available in
Bottles of 30:
Bottles of 90:
Bottles of 500:
300 mg capsules:
White to off white powder filled in size “0” hard gelatin capsules with orange opaque colored cap and white opaque colored body imprinted “SG” on cap and “357” on body with black ink; available in
Bottles of 30:
Bottles of 90:
Bottles of 500:
Storage and Handling
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].

14.1 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The efficacy of the maximum recommended dose of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three

double-blind, placebo-controlled, multicenter studies with three times a day dosing, two of which studied the maximum recommended dose. Patients were enrolled with either Type 1 or Type 2 diabetes mellitus and a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. A total of 89% of patients completed Studies DPN 1 and DPN 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 6.1 to 6.7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study DPN 1: This 5-week study compared pregabalin 25 mg, 100 mg, or 200 mg three times a day with placebo. Treatment with pregabalin 100 mg and 200 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. There was no evidence of a greater effect on pain scores of the 200 mg three times a day dose than the 100 mg three times a day dose, but there was evidence of dose dependent adverse reactions [see ADVERSE REACTIONS (6.1)]. For a range of levels of improvement in pain intensity from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. 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 1: Patients Achieving Various Levels of Improvement in Pain Intensity – Study DPN 1

[Figure 1]

Study DPN 2: This 8-week study compared pregabalin 100 mg three times a day with placebo. Treatment with pregabalin 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. 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 2: Patients Achieving Various Levels of Improvement in Pain Intensity– Study DPN 2

[Figure 2]

14.2 Postherpetic Neuralgia

The efficacy of pregabalin for the management of postherpetic neuralgia was established in three double-blind, placebo-controlled, multicenter studies. These studies enrolled patients with neuralgia persisting for at least 3 months following healing of herpes zoster rash and a minimum baseline 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). Seventy-three percent of patients completed the studies. The baseline mean pain scores

across the 3 studies ranged from 6 to 7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study PHN 1: This 13-week study compared pregabalin 75 mg, 150 mg, and 300 mg twice daily with placebo. Patients with creatinine clearance (CLcr) between 30 mL/min to 60 mL/min were randomized to 75 mg, 150 mg, or placebo twice daily. Patients with creatinine clearance greater than 60 mL/min were randomized to 75 mg, 150 mg, 300 mg or placebo twice daily. In patients with creatinine clearance greater than 60 mL/min treatment with all doses of pregabalin statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Despite differences in dosing based on renal function, patients with creatinine clearance between 30 mL/min to 60 mL/min tolerated pregabalin less well than patients with creatinine clearance greater than 60 mL/min as evidenced by higher rates of discontinuation due to adverse reactions. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 3 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. 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 3: Patients Achieving Various Levels of Improvement in Pain Intensity– Study PHN 1

[Figure 3]

Study PHN 2: This 8-week study compared pregabalin 100 mg or 200 mg three times a day with placebo, with doses assigned based on creatinine clearance. Patients with creatinine clearance between 30 mL/min to 60 mL/min were treated with 100 mg three times a day, and patients with creatinine clearance greater than 60 mL/min were treated with 200 mg three times daily. Treatment with pregabalin statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 4 shows the fraction of patients achieving those levels of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. 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 4: Patients Achieving Various Levels of Improvement in Pain Intensity – Study PHN 2

[Figure 4]

Study PHN 3: This 8-week study compared pregabalin 50 mg or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with pregabalin 50 mg and 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Patients with creatinine clearance between 30 mL/min to 60 mL/min tolerated pregabalin less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of

discontinuation due to adverse reactions. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. 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 5: Patients Achieving Various Levels of Improvement in Pain Intensity– Study PHN 3

[Figure 5]

14.3 Adjunctive Therapy for Partial-Onset Seizures in Patients 17 Years of Age and Older

Adjunctive Therapy for Partial-Onset Seizures in Adult Patients

The efficacy of pregabalin as adjunctive therapy for partial-onset seizures in adult patients was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter studies. Patients were enrolled who had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs). Patients taking gabapentin were required to discontinue gabapentin treatment 1 week prior to entering baseline. 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 25 years in these 3 studies and the mean and median baseline seizure frequencies were 22.5 and 10 seizures per month, respectively. Approximately half of the patients were taking 2 concurrent AEDs at baseline. Among the pregabalin -treated patients, 80% completed the double-blind phase of the studies.

Table 11 shows median baseline seizure rates and median percent reduction in seizure frequency by dose.

Table 11. Seizure Response in Controlled, Adjunctive Epilepsy Studies in Adults

Daily Dose of Pregabalin	Dosing Regimen	N	Baseline Seizure Frequency/mo Median	% Change from Baseline p-value, vs. placebo
Study E1				
Placebo	BID	100	9.5	0
50 mg/day	BID	88	10.3	-9 0.4230
150 mg/day	BID	86	8.8	-35 0.0001
300 mg/day	BID	90	9.8	-37 0.0001
600 mg/day	BID	89	9.0	-51 0.0001
Study E2				
Placebo	TID	96	9.3	1
150 mg/day	TID	99	11.5	-17 0.0007
600 mg/day	TID	92	12.3	-43 0.0001
Study E3				
Placebo	BID/TID	98	11	-1
600 mg/day	BID	103	9.5	-36 0.0001
600 mg/day	TID	111	10	-48 0.0001

In the first study (E1), there was evidence of a dose-response relationship for total daily doses of pregabalin between 150 mg/day and 600 mg/day; a dose of 50 mg/day was not effective. In the first study (E1), each daily dose was divided into two equal doses

(twice a day dosing). In the second study (E2), each daily dose was divided into three equal doses (three times a day dosing). In the third study (E3), the same total daily dose was divided into two equal doses for one group (twice a day dosing) and three equal doses for another group (three times a day dosing). While the three times a day dosing group in Study E3 performed numerically better than the twice a day dosing group, this difference was small and not statistically significant.

A secondary outcome measure included the responder rate (proportion of patients with greater than or equal to 50% reduction from baseline in partial seizure frequency). The following figure displays responder rate by dose for two of the studies.

Figure 6: Responder Rate by Adjunctive Epilepsy Study

[Figure 6]

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

[Figure 7]

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

Pediatric use information is approved for Pfizer’s LYRICA (pregabalin) Capsules and Oral Solution products. However, due to Pfizer’s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

14.4 Management of Fibromyalgia

The efficacy of pregabalin 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 pregabalin 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 pregabalin 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 14.

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

[Figure 9]

Table 14. Patient Global Response in Fibromyalgia Study F1

Patient Global Impression of Change Treatment Group (mg/day)	% Any Improvement	95% CI
PGB = Pregabalin		
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)

Study F2: This randomized withdrawal study compared pregabalin 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 pregabalin during the 6-week open-label phase. Of the patients entering the randomized treatment phase assigned to remain on pregabalin, 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 pregabalin 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 pregabalin also resulted in a longer time to loss of response based on the FIQ1, and longer time to loss of overall assessment of patient status, as measured by the PGIC2.

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)

[Figure 10]

14.5 Management of Neuropathic Pain Associated with Spinal Cord Injury

The efficacy of pregabalin 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 mg/day to 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 pregabalin 150 mg/day to 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

[Figure 11]

Study SCI 2: This 16-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, flexible dose (150 mg/day to 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 pregabalin 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

[Figure 12]

Pregabalin is described chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is C8H17NO2 and the molecular weight is 159.23. The chemical structure of pregabalin is:

Chemical Structure
Pregabalin is a white to off-white, crystalline powder with a pKa1 of 4.2 and a pKa2 of 10.6. It is sparingly soluble in water. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.35.

Pregabalin Capsules are administered orally and are supplied as imprinted hard-shell capsules containing 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg of pregabalin, along with pregelatinized starch and talc as inactive ingredients. The capsule shells contain gelatin, titanium dioxide and sodium lauryl sulfate. In addition, the orange capsule shells (75 mg, 100 mg, 200 mg, 225 mg and 300 mg strengths) contain the colorants FD&C Blue 1, FD&C Red 40 and FD&C Yellow 6. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

In the postmarketing experience, the most commonly reported adverse events observed with pregabalin when taken in overdose include reduced consciousness, depression/anxiety, confusional state, agitation, and restlessness. Seizures and heart block have also been reported. Deaths have been reported in the setting of lone pregabalin overdose and in combination with other CNS depressants.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observe usual precautions to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. Contact a Certified Poison Control Center for up-to-date information on the management of overdose with pregabalin.

Pregabalin can be removed by hemodialysis. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

9.1 Controlled Substance
Pregabalin is a Schedule V controlled substance.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

9.2 Abuse
In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, pregabalin (450 mg, single dose) received subjective ratings of “good drug effect,” “high” and “liking” to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of pregabalin-treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.

9.3 Dependence
In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see WARNINGS AND PRECAUTIONS (5.6)], consistent with physical dependence. In the post-marketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.

The following serious adverse reactions are described elsewhere in the labeling:
Angioedema [see WARNINGS AND PRECAUTIONS (5.1)]

Hypersensitivity [see WARNINGS AND PRECAUTIONS (5.2)]
Suicidal Behavior and Ideation [see WARNINGS AND PRECAUTIONS (5.3)]
Respiratory Depression [see WARNINGS AND PRECAUTIONS (5.4)]
Dizziness and Somnolence [see WARNINGS AND PRECAUTIONS (5.5)]
Increased Risk of Adverse Reactions with Abrupt or Rapid Discontinuation [see WARNINGS AND PRECAUTIONS (5.6)]
Peripheral Edema [see WARNINGS AND PRECAUTIONS (5.7)]
Weight Gain [see WARNINGS AND PRECAUTIONS (5.8)]
Tumorigenic Potential [see WARNINGS AND PRECAUTIONS (5.9)]
Ophthalmological Effects [see WARNINGS AND PRECAUTIONS (5.10)]
Creatine Kinase Elevations [see WARNINGS AND PRECAUTIONS (5.11)]
Decreased Platelet Count [see WARNINGS AND PRECAUTIONS (5.12)]
PR Interval Prolongation [see WARNINGS AND PRECAUTIONS (5.13)]

6.1 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 pregabalin, more than 10,000 patients have received pregabalin. 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 pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (4%) and somnolence (4%). In the placebo group, 1% of patients withdrew due to dizziness and less than 1% withdrew due to somnolence. Other adverse reactions that led to discontinuation from controlled trials more frequently in the pregabalin 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 Controlled Clinical Studies in Adults

In premarketing controlled trials of all adult patient populations combined (including DPN, PHN, and adult patients with partial-onset seizures), 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 pregabalin than by subjects treated with placebo (greater than or equal to 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 adults with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% 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 (3%) and somnolence (2%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin 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 4 lists all adverse reactions, regardless of causality, occurring in greater than or equal to 1% of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin 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 4. Adverse Reaction Incidence in Controlled Trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Body system
Preferred term 75 mg/day
[N=77]
% 150 mg/day
[N=212]
% 300 mg/day
[N=321]
% 600 mg/day
[N=369]
% All PGB* Placebo
[N=979]
% [N=459]
%

*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

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
Controlled Studies in Postherpetic Neuralgia
Adverse Reactions Leading to Discontinuation
In clinical trials in adults with postherpetic neuralgia, 14% of patients treated with pregabalin and 7% 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 (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 pregabalin 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 5 lists all adverse reactions, regardless of causality, occurring in greater than or equal to 1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin 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”. Overall, 12.4% of all pregabalin-treated patients and 9.0% of all placebo-treated patients had at least one severe event while 8% of pregabalin-treated patients and 4.3% of placebo-treated patients had at least one severe treatment-related adverse event.
Table 5. Adverse Reaction Incidence in Controlled Trials in Neuropathic Pain Associated with Postherpetic Neuralgia
Body system
Preferred term 75 mg/day
[N=84]
% 150 mg/day
[N=302]
% 300 mg/day
[N=312]
% 600 mg/day
[N=154]
% All PGB*
[N=852]
% Placebo
[N=398]
%
*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

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

Controlled Studies of Adjunctive Therapy for Partial-Onset Seizures in Adult Patients

Adverse Reactions Leading to Discontinuation

Approximately 15% of patients receiving pregabalin and 6% of patients receiving placebo in trials of adjunctive therapy for partial-onset seizures discontinued prematurely due to adverse reactions. In the pregabalin treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, less than 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 pregabalin 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 6 lists all dose-related adverse reactions occurring in at least 2% of all pregabalin-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 pregabalin and 294 patients received placebo for up to 12 weeks. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of “mild” or “moderate”.

Table 6. Dose-related Adverse Reaction Incidence in Controlled Trials of Adjunctive Therapy for Partial-Onset Seizures in Adult Patients

Body System Preferred Term	150 mg/day [N = 185] %	300 mg/day [N = 90] %	600 mg/day [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.‡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 mg/day to 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, less than 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 9 lists all adverse reactions, regardless of causality, occurring in greater than or equal to 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 9. Adverse Reaction Incidence in Controlled Trials in Fibromyalgia

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* Placebo
[N=1517]
% [N=505]
%
*PGB: pregabalin
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
Hypoesthesia 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
Depression 2 2 2 2 2 2
Respiratory, Thoracic and Mediastinal Disorders
Pharyngolaryngeal pain 2 1 3 3 2 2

Controlled Studies in Neuropathic Pain Associated with Spinal Cord Injury

Adverse Reactions Leading to Discontinuation

In clinical trials of adults with neuropathic pain associated with spinal cord injury, 13% of patients treated with pregabalin 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 somnolence (3%) and edema (2%). In comparison, none of the placebo-treated patients withdrew due to somnolence and edema. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue and balance disorder. Each of these adverse reactions led to withdrawal in less than 2% of patients.

Most Common Adverse Reactions

Table 10 lists all adverse reactions, regardless of causality, occurring in greater than or equal to 2% of patients for which the incidence was greater than in the placebo treatment group with neuropathic pain associated with spinal cord injury in the controlled trials. A majority of pregabalin-treated patients in clinical studies experienced adverse reactions with a maximum intensity of "mild" or "moderate".

Table 10. Adverse Reaction Incidence in Controlled Trials in Neuropathic Pain Associated with Spinal Cord Injury

System Organ Class
Preferred term PGB* (N=182) Placebo (N=174)
% %

*PGB: Pregabalin

Ear and labyrinth disorders
Vertigo 2.7 1.1
Eye disorders
Vision blurred 6.6 1.1
Gastrointestinal disorders

Dry mouth 11.0 2.9
Constipation 8.2 5.7
Nausea 4.9 4.0
Vomiting 2.7 1.1
General disorders and administration site conditions
Fatigue 11.0 4.0
Edema peripheral 10.4 5.2
Edema 8.2 1.1
Pain 3.3 1.1
Infections and infestations
Nasopharyngitis 8.2 4.6
Investigations
Weight increased 3.3 1.1
Blood creatine phosphokinase increased 2.7 0
Musculoskeletal and connective tissue disorders
Muscular weakness 4.9 1.7
Pain in extremity 3.3 2.3
Neck pain 2.7 1.1
Back pain 2.2 1.7
Joint swelling 2.2 0
Nervous system disorders
Somnolence 35.7 11.5
Dizziness 20.9 6.9
Disturbance in attention 3.8 0
Memory impairment 3.3 1.1
Paresthesia 2.2 0.6
Psychiatric disorders
Insomnia 3.8 2.9
Euphoric mood 2.2 0.6
Renal and urinary disorders
Urinary incontinence 2.7 1.1
Skin and subcutaneous tissue disorders
Decubitus ulcer 2.7 1.1
Vascular disorders
Hypertension 2.2 1.1
Hypotension 2.2 0

Other Adverse Reactions Observed During the Clinical Studies of Pregabalin

Following is a list of treatment-emergent adverse reactions reported by patients treated with pregabalin 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 (5).

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 effect, Intentional Injury, Retroperitoneal Fibrosis, Shock

Cardiovascular System – Infrequent: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; Rare: ST Depressed, Ventricular Fibrillation

Digestive System – Frequent: Gastroenteritis, Increased appetite; Infrequent: Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; Rare: Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess

Hemic and Lymphatic System – Frequent: Ecchymosis; Infrequent: Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; Rare: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia, Alanine aminotransferase increased, Aspartate aminotransferase increased

Metabolic and Nutritional Disorders – Rare: Glucose Tolerance Decreased, Urate Crystalluria

Musculoskeletal System – Frequent: Arthralgia, Leg cramps, Myalgia, Myasthenia; Infrequent: Arthrosis; Rare: Chondrodystrophy, Generalized Spasm

Nervous System – Frequent: Anxiety, Depersonalization, Hypertonia, Hypoesthesia, Libido decreased, Nystagmus, Paresthesia, Sedation, Stupor, Twitching; Infrequent: Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, Rare: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus

Respiratory System – Rare: Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn

Skin and Appendages – Frequent: Pruritus, Infrequent: Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; Rare: Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule

Special senses – Frequent: Conjunctivitis, Diplopia, Otitis media, Tinnitus; Infrequent: Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; Rare: Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis

Urogenital System – Frequent: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; Infrequent: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; Rare: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse

experience reports by race.
Pediatric use information is approved for Pfizer's LYRICA (pregabalin) Capsules and Oral Solution products. However, due to Pfizer's marketing exclusivity rights, this drug product is not labeled with that pediatric information.
6.2 Post-marketing Experience
The following adverse reactions have been identified during postapproval use of pregabalin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Nervous System Disorders – Headache
Gastrointestinal Disorders – Nausea, Diarrhea
Reproductive System and Breast Disorders – Gynecomastia, Breast Enlargement
Skin and subcutaneous tissue disorders – Bullous pemphigoid
There are postmarketing reports of life-threatening or fatal respiratory depression in patients taking pregabalin with opioids or other CNS depressants, or in the setting of underlying respiratory impairment.
In addition, there are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics.

Pregabalin capsules are indicated for:

• Management of neuropathic pain associated with diabetic peripheral neuropathy

• Management of postherpetic neuralgia

• Adjunctive therapy for the treatment of partial-onset seizures in patients 17 years of age and older

• Management of fibromyalgia

• Management of neuropathic pain associated with spinal cord injury

Pediatric use information is approved for Pfizer's LYRICA (pregabalin) Capsules and Oral Solution products. However, due to Pfizer's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

2.1 Important Administration Instructions
Pregabalin capsules are given orally with or without food.
When discontinuing pregabalin, taper gradually over a minimum of 1 week [see WARNINGS AND PRECAUTIONS (5.6)].
Because pregabalin is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function [see DOSAGE AND ADMINISTRATION (2.7)].
2.2 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy in Adults
The maximum recommended dose of pregabalin capsule is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability.
Although pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended [see ADVERSE REACTIONS (6.1)].

2.3 Postherpetic Neuralgia in Adults
The recommended dose of pregabalin capsule is 75 mg to 150 mg two times a day, or 50 mg to 100 mg three times a day (150mg/day to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 75 mg two times a day, or 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability.
Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate pregabalin, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, reserve dosing above 300 mg/day for those patients who have on-going pain and are tolerating 300 mg daily [see ADVERSE REACTIONS (6.1)].
2.4 Adjunctive Therapy for Partial-Onset Seizures in Patients 17 Years of Age and Older
The recommended dosage for adult patients 17 years of age and older are included in Table 1. Administer the total daily dosage orally in two or three divided doses as indicated in Table 1. Based on clinical response and tolerability, dosage may be increased, approximately weekly.
Table 1: Recommended Dosage for Adult Patients 17 Years and Older
Age and Body Weight Recommended Initial Dosage Recommended Maximum Dosage Frequency of Administration
Adults (17 years and older) 150 mg/day 600 mg/day 2 or 3 divided doses
Both the efficacy and adverse event profiles of pregabalin have been shown to be dose-related.
The effect of dose escalation rate on the tolerability of pregabalin has not been formally studied.
The efficacy of adjunctive pregabalin in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of pregabalin with gabapentin cannot be offered.
Pediatric use information is approved for Pfizer’s LYRICA (pregabalin) Capsules and Oral Solution products. However, due to Pfizer’s marketing exclusivity rights, this drug product is not labeled with that pediatric information.
2.5 Management of Fibromyalgia in Adults
The recommended dose of pregabalin capsules for fibromyalgia is 300 mg/day to 450 mg/day. Begin dosing at 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). Although pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended [see ADVERSE REACTIONS (6.1)].
2.6 Neuropathic Pain Associated with Spinal Cord Injury in Adults
The recommended dose range of pregabalin capsules for the treatment of neuropathic pain associated with spinal cord injury is 150 mg/day to 600 mg/day. The recommended starting dose is 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient pain relief after 2 to 3 weeks of treatment with 150 mg two times a day and who tolerate pregabalin capsules may be treated with up to 300 mg two times a day [see CLINICAL STUDIES (14.5)].
2.7 Dosing for Adult Patients with Renal Impairment

In view of dose-dependent adverse reactions and since pregabalin is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function. The use of pregabalin in pediatric patients with compromised renal function has not been studied.

Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table 2. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

Cockcroft and Gault equation

Next, refer to the Dosage and Administration section to determine the recommended total daily dose based on indication, for a patient with normal renal function (CLcr greater than or equal to 60 mL/min). Then refer to Table 2 to determine the corresponding renal adjusted dose.

(For example: A patient initiating pregabalin therapy for postherpetic neuralgia with normal renal function (CLcr greater than or equal to 60 mL/min), receives a total daily dose of 150 mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a total daily dose of 75 mg/day pregabalin administered in two or three divided doses.)

For patients undergoing hemodialysis, adjust the pregabalin daily dose based on renal function. In addition to the daily dose adjustment, administer a supplemental dose immediately following every 4-hour hemodialysis treatment (see Table 2).

Table 2. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)*	Dose Regimen
Greater than or equal to 60	150 300 450 600	BID or TID
30–60	75 150 225 300	BID or TID
15–30	25–50 75 100–150	150 QD or BID
Less than 15	25 25–50 50–75	75 QD
Supplementary dosage following hemodialysis (mg)†		
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg		
Patients on the 25 mg – 50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg		
Patients on the 50 mg – 75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg		
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg		

TID= Three divided doses; BID = Two divided doses; QD = Single daily dose.

*Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.†Supplementary dose is a single additional dose.

PREGABALIN

pregabalin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72189-328(NDC:50228-356)
Route of Administration	ORAL	**DEA Schedule**	CV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PREGABALIN (UNII: 55JG375S6M) (PREGABALIN - UNII:55JG375S6M)	PREGABALIN	225 mg

Inactive Ingredients

Ingredient Name	Strength
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
SHELLAC (UNII: 46N107B71O)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics

Color	white ((white opaque colored body)) , orange ((light orange colored cap))	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	SG;356
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-328-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	02/21/2022	
2	NDC:72189-328-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	02/21/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA208677	02/21/2022	

Labeler - Direct Rx (079254320)

Registrant - Direct Rx (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
Direct Rx		079254320	repack(72189-328)