**PREGABALIN**

**THERAPEUTICS**

**Brands** • Lyrica  
*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: glutamate voltage-gated calcium channel blocker (Glu-CB)
- Anticonvulsant, antineuralgic for chronic pain, alpha 2 delta ligand at voltage-sensitive calcium channels

**Commonly Prescribed for**  
(bold for FDA approved)
- Diabetic peripheral neuropathy
- Postherpetic neuralgia
- Fibromyalgia
- Neuropathic pain associated with spinal cord injury
- Partial seizures in adults (adjunctive)
- Peripheral neuropathic pain
- Generalized anxiety disorder (GAD)
- Panic disorder
- Social anxiety disorder

**How the Drug Works**
- Is a leucine analogue and is transported both into the blood from the gut and also across the blood-brain barrier into the brain from the blood by the system L transport system (a sodium independent transporter) as well as by additional sodium-dependent amino acid transporter systems
- Binds to the alpha 2 delta subunit of voltage-sensitive calcium channels
- This closes N and P/Q presynaptic calcium channels, diminishing excessive neuronal activity and neurotransmitter release
- Although structurally related to gamma-aminobutyric acid (GABA), no known direct actions on GABA or its receptors

**How Long Until It Works**
- Can reduce neuropathic pain and anxiety within a week
- Should reduce seizures by 2 weeks
- If it is not producing clinical benefits within 6–8 weeks, it may require a dosage increase or it may not work at all

**If It Works**
- The goal of treatment of neuropathic pain, seizures, and anxiety disorders is to reduce symptoms as much as possible, and if necessary in combination with other treatments
- Treatment of neuropathic pain most often reduces but does not eliminate all symptoms and is not a cure since symptoms usually recur after medicine stopped
- Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists

**If It Doesn’t Work (for neuropathic pain)**
- Many patients have only a partial response where some symptoms are improved but others persist
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider biofeedback or hypnosis for pain
- Consider psychotherapy for anxiety
- Consider the presence of noncompliance and counsel patient
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- In addition to being a first-line treatment for neuropathic pain and anxiety disorders, pregabalin is itself an augmenting agent to numerous other anticonvulsants in treating epilepsy
- For postherpetic neuralgia, pregabalin can decrease concomitant opiate use
- For neuropathic pain, TCAs and SNRIs as well as tiagabine, other anticonvulsants, and even opiates can augment pregabalin if done by experts while carefully monitoring in difficult cases
- For anxiety, SSRIs, SNRIs, or benzodiazepines can augment pregabalin

**Tests**
- None for healthy individuals
### DOSSING AND USE

#### Usual Dosage Range
- 150–600 mg/day in 2–3 doses

#### Dosage Forms
- Capsule 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg

#### How to Dose
- Neuropathic pain: initial 150 mg/day in 2–3 doses; can increase to 300 mg/day in 2–3 doses after 7 days; can increase to 600 mg/day in 2–3 doses after 7 more days; maximum dose generally 600 mg/day (may be lower for diabetic peripheral neuropathy and fibromyalgia)
- Seizures: initial 150 mg/day in 2–3 doses; can increase to 300 mg/day in 2–3 doses after 7 days; can increase to 600 mg/day in 2–3 doses after 7 more days; maximum dose generally 600 mg/day

### SIDE EFFECTS

#### How Drug Causes Side Effects
- CNS side effects may be due to excessive blockade of voltage-sensitive calcium channels

#### Notable Side Effects
- Sedation, dizziness
- Ataxia, fatigue, tremor, dysarthria, paresthesia, memory impairment, coordination abnormal, impaired attention, confusion, euphoric mood, irritability
- Vomiting, dry mouth, constipation, weight gain, increased appetite, flatulence
- Blurred vision, diplopia
- Peripheral edema
- Libido decreased, erectile dysfunction

#### Life-Threatening or Dangerous Side Effects
- Rare activation of suicidal ideation and behavior (suicidality)

#### Weight Gain
- Occurs in significant minority

#### Sedation
- Many experience and/or can be significant in amount
- Dose-related
- Can wear off with time

#### What to Do About Side Effects
- Wait
- Wait
- Wait
- Take more of the dose at night to reduce daytime sedation
- Lower the dose
- Switch to another agent

#### Best Augmenting Agents for Side Effects
- Many side effects cannot be improved with an augmenting agent

#### Dosing Tips
- Generally given in one-third to one-sixth the dose of gabapentin
- If pregabalin is added to a second sedating agent, such as another anticonvulsant, a benzodiazepine, or an opiate, the titration period should be at least a week to improve tolerance to sedation
- Most patients need to take pregabalin only twice daily
- At the high end of the dosing range, tolerability may be enhanced by splitting dose into 3 or more divided doses
- For intolerable sedation, can give most of the dose at night and less during the day
- To improve slow-wave sleep, may only need to take pregabalin at bedtime
- May be taken with or without food

#### Overdose
- No fatalities

#### Long-Term Use
- Safe

#### Habit Forming
- No

#### How to Stop
- Taper over a minimum of 1 week
PREGABALIN

• Epilepsy patients may seize upon withdrawal, especially if withdrawal is abrupt
• Discontinuation symptoms uncommon

Pharmacokinetics
• Pregabalin is not metabolized but excreted intact renally
• Elimination half-life approximately 5–7 hours

Drug Interactions
• Pregabalin has not been shown to have significant pharmacokinetic drug interactions
• Because pregabalin is excreted unchanged, it is unlikely to have significant pharmacokinetic drug interactions
• May add to or potentiate the sedative effects of oxycodone, lorazepam, and alcohol

Other Warnings/Precautions
• Dizziness and sedation could increase the chances of accidental injury (falls) in the elderly
• Increased incidence of hemangiosarcoma at high doses in mice involves platelet changes and associated endothelial cell proliferation not present in rats or humans; no evidence to suggest an associated risk for humans
• Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such side effects immediately

Do Not Use
• If there is a proven allergy to pregabalin or gabapentin
• If patient has a problem of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption

Renal Impairment
• Pregabalin is renally excreted, so the dose may need to be lowered
• Dosing can be adjusted according to creatinine clearance, such that patients with clearance below 15 mL/min should receive 25–75 mg/day in 1 dose, patients with clearance between 15–29 mL/min should receive 25–150 mg/day in 1–2 doses, and patients with clearance between 30–59 mL/min should receive 75–300 mg/day in 2–3 doses
• Starting dose should be at the bottom of the range; titrate as usual up to maximum dose
• Can be removed by hemodialysis; patients receiving hemodialysis may require a supplemental dose of pregabalin following hemodialysis (25–100 mg)

Hepatic Impairment
• Dose adjustment not necessary

Cardiac Impairment
• No specific recommendations

Elderly
• Some patients may tolerate lower doses better
• Elderly patients may be more susceptible to adverse effects

Children and Adolescents
• Safety and efficacy have not been established
• Use should be reserved for the expert

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
• Antiepileptic Drug Pregnancy Registry: (888) 233–2334
• Taper drug if discontinuing
• Seizures, even mild seizures, may cause harm to the embryo/fetus

SPECIAL POPULATIONS

• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
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611
Breast Feeding

- Unknown if pregabalin is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed
- If drug is continued while breast feeding, infant should be monitored for possible adverse effects
- If infant becomes irritable or sedated, breast feeding or drug may need to be discontinued

Pearls

- First treatment approved for fibromyalgia
- One of the first treatments approved for neuropathic pain associated with diabetic peripheral neuropathy
- Also approved in postherpetic neuralgia
- Improves sleep disruption as well as pain in patients with painful diabetic peripheral neuropathy or postherpetic neuralgia
- Improves sleep disruption as well as pain associated with fibromyalgia
- Well studied in epilepsy, peripheral neuropathic pain, and GAD, and actually approved for GAD in Europe
- Off-label use for GAD, panic disorder, and social anxiety disorder may be justified in the USA
- May have uniquely robust therapeutic actions for both the somatic and the psychic symptoms of GAD
- Off-label use as an adjunct for bipolar disorder may not be justified
- One of the few agents that enhances slow-wave delta sleep, which may be helpful in chronic neuropathic pain syndromes
- Pregabalin is generally well tolerated, with only mild adverse effects
- Although no head-to-head studies, appears to be better tolerated and more consistently efficacious at high doses than gabapentin
- Drug absorption and clinical efficacy may be more consistent at high doses for pregabalin compared to gabapentin because of the higher potency of pregabalin and the fact that, unlike gabapentin, it is transported by more than one transport system

Potential Advantages

- First-line for diabetic peripheral neuropathy
- Fibromyalgia
- Anxiety disorders
- Sleep
- Has relatively mild side effect profile
- Has few pharmacokinetic drug interactions
- More potent and probably better tolerated than gabapentin

Potential Disadvantages

- Requires 2–3 times a day dosing
- Not approved for anxiety disorders in the USA
- Not approved for fibromyalgia in Europe

Primary Target Symptoms

- Seizures
- Pain
- Anxiety

Suggested Reading


