**LEVERTIRACETAM**

**Brands**
- Keppra
- Keppra XR

*see index for additional brand names*

**Generic?** Yes

**Class**
- Anticonvulsant, synaptic vesicle protein SV2A modulator

**Commonly Prescribed for**
(bold for FDA approved)
- Adjunct therapy for partial seizures in patients with epilepsy (≥16 years of age for extended-release, ≥4 years of age for immediate-release)
- Adjunct therapy for myoclonic seizures in juvenile myoclonic epilepsy (ages 12 and older)
- Adjunct therapy for primary generalized tonic-clonic seizures in idiopathic generalized epilepsy (ages 6 and older)
- Neuropathic pain/chronic pain
- Mania

**How the Drug Works**
- Binds to synaptic vesicle protein SV2A, which is involved in synaptic vesicle exocytosis
- Opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells

**How Long Until It Works**
- Should reduce seizures by 2 weeks
- Not yet clear if it has mood-stabilizing effects in bipolar disorder or antineuralgic actions in chronic neuropathic pain, but some patients may respond and if so, would be expected to show clinical effects starting by 2 weeks although it may take several weeks to months to optimize clinical effects

**If It Works**
- The goal of treatment is complete remission of symptoms (e.g., seizures, mania, pain)
- The goal of treatment of chronic neuropathic pain is to reduce symptoms

**If It Doesn’t Work (for bipolar disorder or neuropathic pain)**
- May be effective only in a subset of bipolar patients, in some patients who fail to respond to other mood stabilizers, or it may not work at all
- Many patients have only a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of pain or mood
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose or switching to another agent with better demonstrated efficacy in bipolar disorder or neuropathic pain

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Levetiracetam is itself a second-line augmenting agent to numerous other anticonvulsants, lithium, and atypical antipsychotics for bipolar disorder and to gabapentin, tiagabine, other anticonvulsants, SNRIs, and TCAs for neuropathic pain

**Tests**
- None for healthy individuals

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**THERAPEUTICS**

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**SIDE EFFECTS**

**How Drug Causes Side Effects**
- CNS side effects may be due to excessive actions on SV2A synaptic vesicle proteins or to actions on various voltage-sensitive ion channels

**Notable Side Effects**
- Sedation, dizziness, ataxia, asthenia
LEVETIRACETAM (continued)

- Hematologic abnormalities (decrease in red blood cell count and hemoglobin)

**Life-Threatening or Dangerous Side Effects**
- Rare severe dermatologic reactions [Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)]
- Activation of suicidal ideation and acts (rare)
- Changes in behavior (aggression, agitation, anxiety, hostility)
- Rare activation of suicidal ideation and behavior (suicidality)

**Weight Gain**
- Reported but not expected

**Sedation**
- Many experience and/or can be significant in amount

**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

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**DOSING AND USE**

**Usual Dosage Range**
- 1,000–3,000 mg/day in 2 doses

**Dosage Forms**
- Tablet 250 mg, 500 mg, 750 mg
- Extended-release tablet 500 mg, 750 mg
- Oral solution 100 mg/mL

**How to Dose**
- Initial 1,000 mg/day in 1 (extended-release) or 2 (immediate-release) doses; after 2 weeks can increase by 1,000 mg/day every 2 weeks; maximum dose generally 3,000 mg/day

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**Dosing Tips**
- For intolerable sedation, can give most of the dose at night and less during the day
- Some patients may tolerate and respond to doses greater than 3,000 mg/day

**Overdose**
- No fatalities; sedation, agitation, aggression, respiratory depression, coma

**Long-Term Use**
- Safe
- Habit Forming
- No

**How to Stop**
- Taper
- Epilepsy patients may seize upon withdrawal, especially if withdrawal is abrupt
- Rapid discontinuation can increase the risk of relapse in bipolar disorder
- Discontinuation symptoms uncommon

**Pharmacokinetics**
- Elimination half-life approximately 6–8 hours
- Inactive metabolites
- Not metabolized by CYP450 enzymes
- Does not inhibit/induce CYP450 enzymes
- Renally excreted

**Drug Interactions**
- Because levetiracetam is not metabolized by CYP450 enzymes and does not inhibit or induce CYP450 enzymes, it is unlikely to have significant pharmacokinetic drug interactions

**Other Warnings/Precautions**
- Depressive effects may be increased by other CNS depressants (alcohol, MAOIs, other anticonvulsants, etc.)
- Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such side effects immediately
Monitor patients for behavioral symptoms (agression, agitation, anger, anxiety, apathy, depression, hostility, irritability) as well as for possible psychotic symptoms or suicidality

Do Not Use
- If there is a proven allergy to levetiracetam

**SPECIAL POPULATIONS**

**Renal Impairment**
- Recommended dose for patients with mild impairment may be between 500 mg and 1,500 mg twice a day
- Recommended dose for patients with moderate impairment may be between 250 mg and 750 mg twice a day
- Recommended dose for patients with severe impairment may be between 250 mg and 500 mg twice a day
- Patients on dialysis may require doses between 500 mg and 1,000 mg once a day, with a supplemental dose of 250–500 mg following dialysis

**Hepatic Impairment**
- Dose adjustment usually 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 not established under age 16
- Children may require higher doses than adults; dosing should be adjusted according to weight

**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
- Lack of convincing efficacy for treatment of bipolar disorder or chronic neuropathic pain suggests risk/benefit ratio is in favor of discontinuing levetiracetam during pregnancy for these indications
  ✽ For bipolar patients, given the risk of relapse in the postpartum period, mood-stabilizer treatment, especially with agents with better evidence of efficacy than levetiracetam, should generally be restarted immediately after delivery if patient is unmedicated during pregnancy
  ✽ For bipolar patients, levetiracetam should generally be discontinued before anticipated pregnancies
  ✽ Atypical antipsychotics may be preferable to levetiracetam if treatment of bipolar disorder is required during pregnancy
- Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary

**Breast Feeding**
- Some drug is found in mother’s 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
  ✽ Bipolar disorder may recur during the postpartum period, particularly if there is a history of prior postpartum episodes of either depression or psychosis

- For atypical antipsychotics
- For mood-stabilizer treatment
- For seizures, even mild seizures
- For absence of convincing efficacy
- For bipolar disorder
- For chronic neuropathic pain
- For lack of convincing efficacy of levetiracetam
- For relapse in the postpartum period
- For mood-stabilizer treatment
- For better evidence of efficacy in antiepileptic drugs
- For bipolar disorder
- For unmedicated during pregnancy
- For anticipated pregnancies
- For atypical antipsychotics
- For bipolar disorder
- For recurrence or worsening of bipolar symptoms
- For treatment in the postpartum period
- For history of prior postpartum episodes

LEVETIRACETAM (continued)

Relapse rates may be lower in women who receive prophylactic treatment for postpartum episodes of bipolar disorder
• Atypical antipsychotics and anticonvulsants such as valproate may be safer than levetiracetam during the postpartum period when breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Primary Target Symptoms
• Seizures
• Pain
• Mania

Pearls
• Well studied in epilepsy
• Off-label use second-line and as an augmenting agent may be justified for bipolar disorder and neuropathic pain unresponsive to other treatments
• Unique mechanism of action suggests utility where other anticonvulsants fail to work
• Unique mechanism of action as modulator of synaptic vesicle release suggests theoretical utility for clinical conditions that are hypothetically linked to excessively activated neuronal circuits, such as anxiety disorders and neuropathic pain as well as epilepsy

Potential Advantages
• Patients on concomitant drugs (lack of drug interactions)
• Treatment-refractory bipolar disorder
• Treatment-refractory neuropathic pain

Potential Disadvantages
• Patients noncompliant with twice daily dosing
• Efficacy for bipolar disorder or neuropathic pain not well documented

Suggested Reading


