ZONISAMIDE

**Brands**
- Zonegran

**Generic?**
- Not in U.S.

**Class**
- Antiepileptic drug (AED), structurally a sulfonamide

**Commonly Prescribed For**
(FDA approved in bold)
- Migraine prophylaxis
- Neuropathic pain
- Partial-onset seizures (adjunctive in adults)
- Partial-onset seizures (adjunctive in pediatric patients)
- Obesity
- Bipolar disorder
- Binge-eating disorder/bulimia
- Parkinson’s disease

**How the Drug Works**
- Unknown but there are multiple mechanisms of action that may be important
- Sodium channel antagonist
- Modulates T-type calcium channels
- Binds to GABA receptors
- Weak carbonic anhydrase inhibitor
- MAO-B inhibition
- May help facilitate dopamine and serotonin neurotransmission

**How Long until It Works**
- Seizures: by 2–3 weeks
- Migraines: can take up to 3 months on a stable dose to see full effect

**If It Works**
- Seizures: goal is the remission of seizures. Continue as long as effective and well-tolerated. Consider tapering and slowly stopping after 2 years seizure-free, depending on the type of epilepsy
- Migraine: goal is a 50% or greater reduction in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if patient considering pregnancy

**If it Doesn’t Work**
- Increase to highest tolerated dose
- Migraine: address other issues such as medication-overuse, other coexisting medical disorders, such as anxiety, and consider changing to another agent or adding a second agent

**Best Augmenting Combos for Partial Response or Treatment-Resistance**
- For some patients with epilepsy or migraine, low-dose polytherapy with two or more drugs may be better tolerated and more effective than high-dose monotherapy
- Migraine: consider beta-blockers, antidepressants, natural products, other AEDs, and nonmedication treatments, such as biofeedback, to improve headache control

**Tests**
- Mild to moderate decreases in bicarbonate can occur with zonisamide, but are uncommon reasons for discontinuation
- Routine screening for metabolic acidosis is not recommended

**ADVERSE EFFECTS (AEs)**

**How Drug Causes AEs**
- CNS AEs may be caused by sodium or calcium channel effects or GABA effects
- Carbonic anhydrase inhibition causes metabolic acidosis and may lead to kidney stones

**Notable AEs**
- Sedation, depression, irritability, fatigue, ataxia
- Anorexia, abdominal pain, nausea
- Kidney stones

**Life-Threatening or Dangerous AEs**
- Metabolic acidosis
- Increased BUN and creatinine (nonprogressive)
- Kidney stones (calcium or urate)
- Blood dyscrasias (aplastic anemia or agranulocytosis)
- Rare serious allergic rash (Stevens–Johnson syndrome)
- Fever, dehydration and oligohidrosis (more common in children)
Weight Gain
- Unusual

Sedation
- Common

What to Do about AEs
- May decrease after a longer time on a stable dose
- Paresthesias may respond to high potassium diets
- A small decrease in dose may improve AEs

Best Augmenting Agents for AEs
- Paresthesias may improve with high potassium diet
- Other AEs are more likely to improve by lowering dose

**Dosing and Use**

**Usual Dosage Range**
- Epilepsy: 100–600 mg/day in adults
- Migraine/neuropathic pain: 50–600 mg/day.
  - Once daily dosing is fine
- Parkinson’s disease: used as low-dose adjunctive medication, typically 25–100 mg/day

**Dosage Forms**
- Capsules: 25 mg, 50 mg, 100 mg

**How to Dose**
- In adults, start at low dose (25–50 mg/day for migraine). After 1 week, increase to 100 mg/day. Wait at least 2 weeks before increasing to 200 mg and for each new increase

**Dosing Tips**
- AEs increase with dose increases but can be delayed due to the long half-life of the drug
- Weight loss is often dose-related
- Slow titration can help minimize sedation and other AEs

**Overdose**
- Nystagmus, drowsiness, slurred speech, blurred vision, diplopia, stupor, hypotension, and bradycardia, respiratory depression, and metabolic acidosis. No reported deaths except with multidrug overdoses

**Long-Term Use**
- Safe for long-term use

**Habit Forming**
- No

**How to Stop**
- Taper slowly
- Abrupt withdrawal can lead to seizures in patients with epilepsy. Tremor is also common
- Headaches may return within days to months of stopping

**Pharmacokinetics**
- Majority is renally excreted
- Metabolized in part by CYP3A4 system
- Plasma half-life is 63 hours

**Drug Interactions**
- Any drug that affects hepatic CYP3A4 can affect zonisamide levels
- CYP3A4 inhibitors such as fluoxetine, fluvoxamine, ketoconazole, clarithromycin, and many antivirals increase zonisamide levels
- CYP3A4 inducers such as phenytoin, phenobarbital, primidone, and especially carbamazepine decrease zonisamide levels
- May interact with carbonic anhydrase inhibitors, increasing risk of kidney stones

**Other Warnings/Precautions**
- CNS AEs increase when taken with other CNS depressants
- Patients taking a ketogenic diet for seizures are more likely to experience severe metabolic acidosis on zonisamide
- Can be associated with severe rash – new-onset rash may be sign of hypersensitivity syndrome
- Any unusual bleeding or bruising, fever, or mouth sores should raise concern for rare blood dyscrasias that can occur with zonisamide

**Do Not Use**
- Proven allergy to zonisamide. Because zonisamide contains a sulfa moiety, it may cause allergy in patients with proven sulfa allergy
**SPECIAL POPULATIONS**

**Renal Impairment**
- Zonisamide is primarily renally excreted and patients with severe renal disease may require a slower titration

**Hepatic Impairment**
- Clearance may be decreased in patients with severe liver disease

**Cardiac Impairment**
- No known effects

**Elderly**
- May be more susceptible to CNS AEs

**Children and Adolescents**
- Approved for children aged 16 and up; little data about its use in younger patients but is used off-label for migraine

**Pregnancy**
- Category C
- Teratogenicity in animal studies but no studies in humans
- Patients taking for conditions other than epilepsy should generally stop zonisamide before considering pregnancy. Migraine usually improves in the last 2 trimesters

**Breast-Feeding**
- Some drug is found in breast milk
- Generally recommendations are to discontinue drug or bottle feed

**THE ART OF PAIN PHARMACOLOGY**

**Potential Advantages**
- Useful for migraine
- Usually causes weight loss, unlike many other medications
- Once-daily dose due to long half-life can increase compliance

**Potential Disadvantages**
- Weight loss in thin patients can be troublesome
- Kidney stones
- Fatigue and other CNS AEs

**Primary Target Symptoms**
- Migraine frequency and severity

**Pearls**
- For migraine, zonisamide may be better tolerated but is less effective than topiramate
- Anecdotal experience suggests utility in the treatment of neuropathic pain, such as diabetic neuropathy
- Recent studies suggest low-dose zonisamide (25 mg) can treat motor symptoms in Parkinson’s disease
- Zonisamide is used for treatment of essential tremor
- Occasionally used to offset weight gain seen with psychotropic agents or to treat binge-eating disorder

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**Suggested Reading**


