ZONISAMIDE

**THERAPEUTICS**

**Brands**
- Zonegran

**Generic?**
Not in US

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

**Commonly Prescribed for**
(FDA approved in bold)
- Partial-onset seizures (adjunctive in adults)
- Partial-onset seizures (adjunctive in pediatric patients)
- Primary generalized tonic-clonic seizures (adjunctive; adults and pediatric patients age 2–16)
- Myoclonic epilepsy, Lennox-Gastaut syndrome
- Infantile spasms (West syndrome)
- Migraine prophylaxis
- Obesity
- Bipolar disorder
- Binge-eating disorder/bulimia
- Neuropathic pain
- 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

**If It Doesn’t Work**
- Increase to highest tolerated dose
- Epilepsy: consider changing to another agent, adding a second agent or referral for epilepsy surgery evaluation
- 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 2 or more drugs may be better tolerated and more effective than high-dose monotherapy
- Epilepsy: keep in mind drug interactions and their effect on levels
- Migraine: consider beta-blockers, antidepressants, natural products, other AEDs, and non-medication 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 (non-progressive)
- 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 or remit after a longer time on a stable dose
- Paresthesias may respond to high potassium diets or potassium tablets
- A small decrease in dose may improve AEs

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

**DOSING AND USE**

**Usual Dosage Range**
- Epilepsy: 100–600 mg/day in adults. Most patients do best at 400 mg or less. One/day dosing is fine
- Migraine: 100–600 mg/day. Most studies use 400 mg
- Parkinson’s disease – used as low-dose adjunctive medication, typically 25–100 mg/day

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

**How to Dose**
- In adults, start at low dose (100 mg/day for epilepsy, or 50 mg/day for migraine). After 1 week, increase to 200 mg/day. Wait at least 2 weeks before increasing to 300 mg and for each new increase
- For children, start at 2–4 mg/kg/day, dosed once or twice daily and increase by 2 mg/kg/day every 1–2 weeks until at maintenance dose of 4–8 mg/kg/day. Maximum pediatric dose 12 mg/kg/day

**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 poly-drug 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 CYP450 3A4 system. Plasma half-life is 63 hours

**Drug Interactions**
- Any drug that affects hepatic CYP3A4 can affect zonisamide levels
- CYP3A4 inhibitors such as nefazodone, 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

May help treat infantile spasms related to tuberous sclerosis, especially if ACTH is ineffective or cannot be used

Pregnancy
• Risk category C. Teratogenic in animal studies but no studies in humans
• Risks of stopping medication must outweigh risk to fetus for patients with epilepsy. Seizures and potential status epilepticus place the woman and fetus at risk and can cause reduced oxygen and blood supply to the womb
• Supplementation with 0.4 mg of folic acid before and during pregnancy is recommended
• 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 mother’s breast milk
• Generally recommendations are to discontinue drug or bottle feed
• Monitor infant for sedation, poor feeding or irritability

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
• Highly effective for epilepsy, useful for migraine. Usually causes weight loss, unlike many other medications. Ability to use once daily 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
• Seizure frequency and severity
• Migraine frequency and severity

Pearls
• For epilepsy, higher doses may be needed. AEs are more common when using in combination with other drugs that can produce CNS symptoms
• For migraine, Zonegran may be better tolerated but is less effective than topiramate

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 epilepsy and migraine
Recent studies suggest low-dose zonisamide (25 mg) can effectively treat motor symptoms in Parkinson’s disease and decrease “off” time, perhaps by facilitation of monoamine transmission.

Zonisamide is used for treatment of essential tremor, but in clinical trials was only of modest benefit.

Early studies suggest utility in the treatment of neuropathic pain, such as diabetic neuropathy.

No proven effectiveness in bipolar disorder, and not a first-line treatment.

Occasionally used to offset weight gain seen with psychotropic agents or to treat binge-eating disorder.

Suggested Reading


