Zonisamide

THERAPEUTICS

Brands • Zonegran • Excegran

see index for additional brand names

Generic? Yes

Class • Anticonvulsant, voltage-sensitive sodium channel modulator; T-type calcium channel modulator; structurally a sulfonamide

Commonly Prescribed for (bold for FDA approved)
• Adjunct therapy for partial seizures in adults with epilepsy
• Bipolar disorder
• Chronic neuropathic pain
• Migraine
• Parkinson’s disease
• Psychotropic drug-induced weight gain
• Binge eating disorder

How the Drug Works
• Unknown
• Modulates voltage-sensitive sodium channels by an unknown mechanism
• Also modulates T-type calcium channels
• Facilitates dopamine and serotonin release
• Inhibits carbonic anhydrase

How Long Until It Works
• Should reduce seizures by 2 weeks
• Onset of action as well as convincing therapeutic efficacy have not been demonstrated for uses other than adjunctive treatment of partial seizures

If It Works
• The goal of treatment is complete remission of symptoms (e.g., seizures, pain, mania, migraine)
• Would currently only be expected to work in a subset of patients for conditions other than epilepsy as an adjunctive treatment to agents with better demonstration of efficacy

If It Doesn’t Work (for conditions other than epilepsy)
• May be effective only in patients who fail to respond to agents with proven efficacy, or it may not work at all

• Consider increasing dose or switching to another agent with better demonstrated efficacy

Best Augmenting Combos for Partial Response or Treatment Resistance
• Zonisamide is itself a second-line augmenting agent to numerous other agents in treating conditions other than epilepsy, such as bipolar disorder, chronic neuropathic pain, and migraine

Tests • Consider baseline and periodic monitoring of renal function

SIDE EFFECTS

How Drug Causes Side Effects
• CNS side effects theoretically due to excessive actions at voltage-sensitive ion channels
• Weak inhibition of carbonic anhydrase may lead to kidney stones
• Serious rash theoretically an allergic reaction

Notable Side Effects
• Sedation, depression, difficulty concentrating, agitation, irritability, psychomotor slowing, dizziness, ataxia
• Headache
• Nausea, anorexia, abdominal pain, vomiting
• Kidney stones
• Elevated serum creatinine and blood urea nitrogen

Life-Threatening or Dangerous Side Effects
• Rare serious rash (Stevens-Johnson syndrome, toxic epidermal necrolysis) (sulfonamide)
• Rare oligohidrosis and hyperthermia (pediatric patients)
• Rare blood dyscrasias (aplastic anemia; agranulocytosis)
• Sudden hepatic necrosis
• Sudden unexplained deaths have occurred (unknown if related to zonisamide use)
• Rare activation of suicidal ideation and behavior (suicidality)
Zonisamide (continued)

**Weight Gain**
- Unusual
- Rare
- Common
- Problematic
- Reported but not expected
- Patients may experience weight loss

**Sedation**
- Unusual
- Rare
- Common
- Problematic
- Many experience and/or can be significant in amount
- Dose-related
- Can wear off with time but may not wear off at high doses

**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 and Use**

**Usual Dosage Range**
- 100–600 mg/day in 1–2 doses

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

**How to Dose**
- Initial 100 mg/day; after 2 weeks can increase to 200 mg/day; dose can be increased by 100 mg/day every 2 weeks if necessary and tolerated; maximum dose generally 600 mg/day; maintain stable dose for at least 2 weeks before increasing dose

**Dosing Tips**
- Most clinical experience is at doses up to 400 mg/day
- No evidence from controlled trials of increasing response over 400 mg/day
- However, some patients may tolerate and respond to doses up to 600 mg/day

**Drug Interactions**
- Agents that inhibit CYP450 3A4 (such as nefazodone, fluvoxamine, and fluoxetine) may decrease the clearance of zonisamide, and increase plasma zonisamide levels, possibly requiring lower doses of zonisamide
- Agents that induce CYP450 3A4 (such as carbamazepine) may increase the clearance of zonisamide and decrease plasma zonisamide levels, possibly requiring higher doses of zonisamide
- Enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, phenobarbital, and primidone) may decrease plasma levels of zonisamide
- Theoretically, zonisamide may interact with carbonic anhydrase inhibitors to increase the risk of kidney stones

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Other Warnings/Precautions

- Depressive effects may be increased by other CNS depressants (alcohol, MAOIs, other anticonvulsants, etc.)
- Use with caution when combining with other drugs that predispose patients to heat-related disorders, including carbonic anhydrase inhibitors and anticholinergics

Life-threatening rashes have developed in association with zonisamide use; zonisamide should generally be discontinued at the first sign of serious rash
- Patient should be instructed to report any symptoms of hypersensitivity immediately (fever; flu-like symptoms; rash; blisters on skin or in eyes, mouth, ears, nose, or genital areas; swelling of eyelids, conjunctivitis, lymphadenopathy)
- Patients should be monitored for signs of unusual bleeding or bruising, mouth sores, infections, fever, and sore throat, as there may be an increased risk of aplastic anemia and agranulocytosis with zonisamide
- 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 zonisamide or sulfonamides

Children and Adolescents

- Cases of oligohidrosis and hyperthermia have been reported
- Not approved for use in children under age 16
- Use in children for the expert only, with close monitoring, after other options have failed

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 conditions other than epilepsy suggests risk/benefit ratio is in favor of discontinuing zonisamide during pregnancy for these indications

Breast Feeding

- Unknown if zonisamide 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 child becomes irritable or sedated, breast feeding or drug may need to be discontinued

SPECIAL POPULATIONS

Renal Impairment
- Zonisamide is primarily renally excreted
- Use with caution
- May require slower titration

Hepatic Impairment
- Use with caution
- May require slower titration

Cardiac Impairment
- No specific recommendations

Elderly
- Some patients may tolerate lower doses better
- Elderly patients may be more susceptible to adverse effects
ZONISAMIDE (continued)

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- Treatment-resistant conditions
- Patients who wish to avoid weight gain

**Potential Disadvantages**
- Poor documentation of efficacy for off-label uses
- Patients noncompliant with twice daily dosing

**Primary Target Symptoms**
- Seizures
- Numerous other symptoms for off-label uses
- Patients with a history of kidney stones

**Pearls**
- Well studied in epilepsy
- *Much off-label use is based upon theoretical considerations rather than clinical experience or compelling efficacy studies*
- Early studies suggest efficacy in binge eating disorder
- Early studies suggest possible efficacy in migraine
- Early studies suggest possible utility in Parkinson’s disease
- Early studies suggest possible utility in neuropathic pain
- Early studies suggest some therapeutic potential for mood stabilizing
- Chronic intake of caffeine may lower brain zonisamide concentrations and attenuate its anticonvulsant effects (based on animal studies)
- *Due to reported weight loss in some patients in trials with epilepsy, some patients with psychotropic-induced weight gain are treated with zonisamide*
- Utility for this indication is not clear nor has it been systematically studied
- Phase II trials for the combination of zonisamide and bupropion as a treatment for obesity have been completed

**Suggested Reading**


