

## IMPORTANT SAFETY INFORMATION

### ZONISADE® (zonisamide oral suspension), 100 mg/5 mL

ZONISADE is indicated as adjunctive therapy for the treatment of partial-onset seizures in adults and pediatric patients 16 years of age and older.

*Inform patients that a calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.*

## ADDITIONAL IMPORTANT SAFETY INFORMATION

### Contraindications

Known hypersensitivity to sulfonamides, zonisamide, or any formulation ingredients.

### Warnings and Precautions

**Potentially fatal reaction to Sulfonamides:** Fatalities have occurred as a result of severe reactions to sulfonamides (ZONISADE is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. If signs of hypersensitivity or other serious reactions occur, discontinue ZONISADE immediately.

**Serious Skin Reaction:** Serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported. Consideration should be given to discontinuing ZONISADE in patients who develop an otherwise unexplained rash. If the drug is not discontinued, patients should be observed frequently. Inform patients about the signs of serious skin reactions.

**Serious Hematologic Events:** Aplastic anemia and agranulocytosis have been reported in patients who received zonisamide treatment. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity:** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multi-organ hypersensitivity, has occurred with zonisamide. Some of these events have been fatal or life-threatening. If signs or symptoms of DRESS are present, the patient should be evaluated immediately. ZONISADE should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

**Oligohidrosis and Hyperthermia in Pediatric Patients:** ZONISADE is not approved for use in pediatric patients below 16 years of age. Pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with ZONISADE should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather. Caution should be used when ZONISADE is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include but are not limited to, carbonic anhydrase inhibitors and drugs with anticholinergic activity.

**Acute Myopia and Secondary Angle Closure Glaucoma:** Acute myopia and secondary angle closure glaucoma have been reported in patients receiving zonisamide. Elevated intraocular pressure can lead to serious sequelae, including permanent vision loss if left untreated. Symptoms typically occur within one month after initiating zonisamide therapy. The primary treatment to reverse symptoms is the discontinuation of zonisamide. Myopia and secondary angle closure glaucoma usually resolve or improve after discontinuation of zonisamide.

**Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including ZONISADE, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any

AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

**Metabolic Acidosis:** Metabolic acidosis was commonly observed in adults and pediatric patients in clinical trials and is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase. Pediatric patients may be more likely to develop metabolic acidosis than adults. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of zonisamide. Measurement of baseline and periodic serum bicarbonate during treatment is recommended. If metabolic acidosis develops, consideration should be given to either dose reduction or discontinuation of therapy using dose tapering.

**Seizures on Withdrawal:** As with other AEDs, abrupt withdrawal of ZONISADE in patients with epilepsy may precipitate increased seizure frequency or status epilepticus. Dose reduction or discontinuation of ZONISADE should be done gradually.

**Teratogenicity:** ZONISADE may cause fetal harm when administered to pregnant women and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential who are given ZONISADE should be advised to use effective contraception.

**Cognitive/Neuropsychiatric Adverse Reactions:** Use of zonisamide was frequently associated with central nervous system-related adverse reactions including psychiatric symptoms, cognitive dysfunction, and somnolence or fatigue.

**Hyperammonemia and Encephalopathy:** Hyperammonemia and encephalopathy have been reported with the postmarketing use of zonisamide. The risks may be increased in patients treated with zonisamide and concomitantly taking valproic acid or topiramate. Measure serum ammonia concentration if signs or symptoms of encephalopathy occur. Hyperammonemia resulting from zonisamide resolves when zonisamide is discontinued. Hyperammonemia from zonisamide may resolve or decrease in severity with a decrease of the daily dose.

**Kidney Stones:** ZONISADE may increase the risk for kidney stones. Instruct patients to stay well hydrated while taking ZONISADE.

**Effect on Renal Function:** ZONISADE can cause an increase in serum creatinine and blood urea nitrogen (BUN). ZONISADE should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in the creatinine/BUN concentration. ZONISADE should not be used in patients with renal failure (estimated [GFR] < 50 mL/min) as there has been insufficient experience concerning drug dosing and toxicity.

**Status Epilepticus:** Status epilepticus has been reported at a rate of 1% across all controlled and uncontrolled epilepsy studies in patients treated with zonisamide.

**Laboratory Tests:** ZONISADE may increase serum chloride and alkaline phosphatase, and decrease serum bicarbonate, phosphorus, calcium, and albumin. Clinical management should include a periodic assessment of laboratory values.

## **Adverse Reactions**

The most common adverse reactions with ZONISADE (an incidence at least 4% greater than placebo) in controlled clinical trials and shown in descending order of frequency were somnolence, anorexia, dizziness, ataxia, agitation/irritability, and difficulty with memory and/or concentration.

## **Drug Interactions**

ZONISADE should be used with caution if used in combination with alcohol or other CNS depressants.

Concomitant use of ZONISADE with any other carbonic anhydrase inhibitor may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation.

## **USE IN SPECIFIC POPULATIONS**

### **Pregnancy**

ZONISADE may cause serious adverse fetal effects, based on clinical and nonclinical data.

Advise pregnant patients to enroll in the NAAED Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334 and must be done by patients themselves.

### **Lactation**

Zonisamide is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ZONISADE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **Female and Males of Reproductive Potential**

Based on animal data, ZONISADE can cause fetal harm when administered to a pregnant woman, and female fertility may be compromised with ZONISADE.

### **Pediatric Use**

The safety and effectiveness of ZONISADE in pediatric patients below the age of 16 have not been established.

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**The Important Safety Information does not include all the information needed to use ZONISADE safely and effectively. For additional safety information, please see the accompanying full Prescribing Information for [ZONISADE](#).**

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**To report SUSPECTED ADVERSE REACTIONS, contact Azurity Pharmaceuticals, Inc. at 1-800-461-7449, or FDA at 1-800-FDA-1088 or [www.fda.gov/MedWatch](http://www.fda.gov/MedWatch).**

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