NEW DRUG APPROVAL

Brand Name	Zonisade™
Generic Name	zonisamide
Drug Manufacturer	Azurity Pharmaceuticals, Inc

New Drug Approval

FDA approval date: July 15, 2022

Review designation: Standard

Type of review: Type 3 - New Dosage Form; New Drug Application (NDA): 214273

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Epilepsy is a chronic disease of the brain characterized by an enduring (i.e., persisting) predisposition to generate seizures, unprovoked by any immediate central nervous system insult, and by the neurobiologic, cognitive, psychological, and social consequences of seizure recurrences.

Epilepsy affects both sexes and all ages with worldwide distribution. Globally, an estimated 65 million people suffer from epilepsy. The prevalence and the incidence of epilepsy are slightly higher in men compared to women and tend to peak in the elderly, reflecting the higher frequency of stroke, neurodegenerative diseases, and tumors in this age-group. Focal seizures are more common than generalized seizures both in children and in adults. The etiology of epilepsy varies according to the sociodemographic characteristics of the affected populations and the extent of the diagnostic workup, but a documented cause is still lacking in about 50% of cases from high-income countries (HIC). The overall prognosis of epilepsy is favorable in the majority of patients when measured by seizure freedom. Reports from low/middle-income countries (LMIC; where patients with epilepsy are largely untreated) give prevalence and remission rates that overlap those of HICs. As the incidence of epilepsy appears higher in most LMICs, the overlapping prevalence can be explained by misdiagnosis, acute symptomatic seizures and premature mortality. Studies have consistently shown that about one-half of cases tend to achieve prolonged seizure remission. However, more recent reports on the long-term prognosis of epilepsy have identified differing prognostic patterns, including early and late remission, a relapsing-remitting course, and even a worsening course (characterized by remission followed by relapse and unremitting seizures). Epilepsy per se carries a low mortality risk, but significant differences in mortality rates are expected when comparing incidence and prevalence studies, children and adults, and persons with idiopathic and symptomatic seizures. Sudden unexplained death is most frequent in people with generalized tonic-clonic seizures, nocturnal seizures, and drug refractory epilepsy.

Focal seizures are also called partial seizures since they begin in one area of the brain. They can be caused by any type of focal injury that leaves scar tangles. Medical history or MRI will identify a cause (such as trauma, stroke or meningitis) in about half of the people who have focal seizures. Developmental scars — ones that occur as part of fetal and early growth of the brain — are common causes of focal seizures in children.

Focal seizures can start in one part of the brain and spread to other areas, causing symptoms that are mild or severe, depending on how much of the brain becomes involved.

Focal seizures can evolve into major events that spread to the entire brain and cause tonic-clonic seizures. These seizures are important to treat and prevent since they can cause respiratory problems and injuries.

Efficacy

The efficacy of Zonisade™ is based upon a bioavailability study comparing Zonisade™ oral suspension to zonisamide capsules in healthy subjects. The clinical studies information described below pertains to the zonisamide capsule formulation. The effectiveness of zonisamide as adjunctive therapy has been established in three multicentre, placebo-controlled, double blind, 3-month clinical trials (two domestic, one European) in 499 patients with refractory partial-onset seizures with or without secondary generalization. Each patient had a history of at least four partial-onset seizures per month in spite of receiving one or two ant epilepsy drugs at therapeutic concentrations. The 499 patients (209 women, 290 men) had a mean age of about 35 years. In the two US studies, over 80% of patients were Caucasian; 100% of patients in the European study were Caucasian. zonisamide capsules or placebo was added to the existing therapy. The primary measure of effectiveness was median percent reduction from baseline in partial seizure frequency. The secondary measure was proportion of patients achieving a 50% or greater seizure reduction from baseline (responders). The results described below are for all partial seizures in the intent-to-treat populations. In the first study (n = 203), all patients had a 1-month baseline observation period, then received placebo or zonisamide capsules in one of two dose escalation regimens; either 1) 100 mg/day for five weeks, 200 mg/day for one week, 300 mg/day for one week, and then 400 mg/day for five weeks; or 2) 100 mg/day for one week, followed by 200 mg/day for five weeks, then 300 mg/day for one week, then 400 mg/day for five weeks. This design allowed a 100 mg vs. placebo comparison over weeks 1–5, and a 200 mg vs. placebo comparison over weeks 2–6; the primary comparison was 400 mg (both escalation groups combined) vs. placebo over weeks 8–12. The total daily dose was given as twice a day dosing. Statistically significant treatment differences favoring zonisamide were seen for doses of 100, 200, and 400 mg/day. In the second (n = 152) and third (n = 138) studies, patients had a 2–3-month baseline, then were randomly assigned to placebo or zonisamide capsules for three months. zonisamide was introduced by administering 100 mg/day for the first week, 200 mg/day the second week, then 400 mg/day for two weeks, after which the dose could be adjusted as necessary to a maximum dose of 20 mg/kg/day or a maximum plasma level of 40 µg/mL. In the second study, the total daily dose was given as twice a day dosing; in the third study, it was given as a single daily dose. The average final maintenance doses received in the studies were 530 and 430 mg/day in the second and third studies, respectively. Both studies demonstrated statistically significant differences favoring zonisamide for doses of 400–600 mg/day, and there was no apparent difference between once daily and twice daily dosing (in different studies). Analysis of the data (first 4 weeks) during titration demonstrated statistically significant differences favoring zonisamide at doses between 100 and 400 mg/day. The primary comparison in both trials was for any dose over Weeks 5–12.

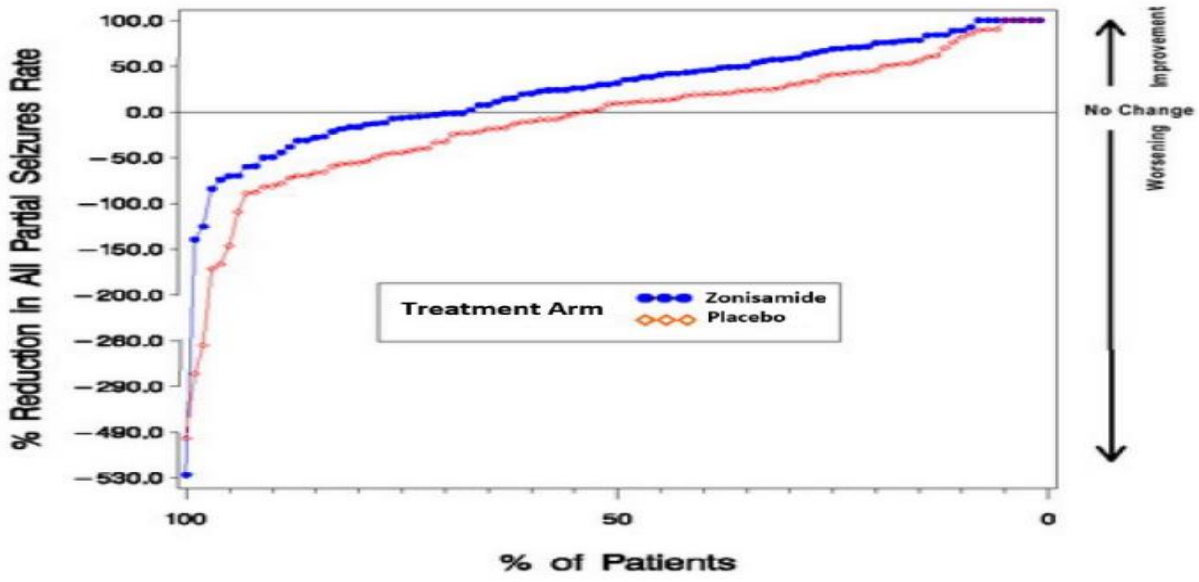
Table 1. Median % Reduction in All Partial-Onset Seizures and % Responders in Primary Efficacy Analyses: Intent-To-Treat Analysis

Study	Median %Reduction in Partial-Onset Seizures		% Responders	
	zonisamide Capsules	Placebo	zonisamide Capsules	Placebo
Study 1:	n=98	n=72	n=98	n=72
Weeks 8-12:	40.5%*	9.0%	41.8%*	22.2%
Study 2:	n=69	n=72	n=69	n=72
Weeks 5-12:	29.6%*	-3.2%	29.0%	15.0%
Study 3:	n=67	n=66	n=67	n=66
Weeks 5-12:	27.2%*	-1.1%	28.0%*	12.0%
* p<0.05 compared to placebo				

Table 2. Median % Reduction in All Partial-Onset Seizures and % Responders for Dose Analyses in Study 1: Intent-To-Treat Analysis				
Dose Group	**Median % Reduction in Partial-Onset Seizures**		**% Responders**	
	zonisamide Capsules	Placebo	zonisamide Capsules	Placebo
100-400 mg/day:	n=112	n=83	n=112	n=83
Weeks 1-12:	32.3%*	5.6%	32.1%*	9.6%
100 mg/day:	n=56	n=80	n=56	n=80
Weeks 1-5:	24.7%*	8.3%	25.0%*	11.3%
200 mg/day:	n=55	n=82	n=55	n=82
Weeks 2-6:	20.4%*	4.0%	25.5%*	9.8%
* p<0.05 compared to placebo				

In Figure 1, a positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in seizure rate), while a negative value indicates a worsening from baseline (i.e., an increase in seizure rate). Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure rate was consistently higher for the zonisamide groups compared to the placebo groups. For example, Figure 1 indicates that approximately 27% of patients treated with zonisamide experienced a 75% or greater reduction, compared to approximately 12% in the placebo groups.

Figure 1. Proportion of Patients Achieving Differing Levels of Seizure Reduction in Zonisamide and Placebo Groups in Studies 2 and 3



No differences in efficacy based on age, sex, or race, as measured by a change in seizure frequency from baseline, were detected.

Safety

ADVERSE EVENTS

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.

WARNINGS & PRECAUTIONS

- Potentially Fatal Reactions to Sulfonamides: Fatalaties have occurred as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, tocix epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias.
- Serious Skin Reactions: Discontinue Zonisade™ at the first sign of rash unless clearly not drug related.
- Serious Hematologic Events: Aplastic anemia and agranulocytosis,has been reported with zonisamide treatment.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity: DRESS also known as multiorgan hypersensitivity, has occurred with zonisamide.
- Oligohidrosis and Hyperthermia in Pediatric Patients: Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients.
- Acute Myopia and Secondary Angle Closure Glaucoma: If occurs, primary treatment is discontinuation of Zonisade™.
- Suicidal Behaviour and Ideation: Monitor patients for suicidal behaviour or ideation.
- Metabolic Acidosis: Baseline and periodic measurement of serum bicarbonate is recommended; consider dose reduction or discontinuation if appropriate.
- Seizures on Withdrawal of Antiepileptic Drugs: Withdraw Zonisade™ gradually.
- Teratogenicity: Based on animal data, may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during Zonisade™ treatment and for one month after discontinuation.

CONTRAINDICATIONS

Zonisade™ is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide.

Clinical Pharmacology

MECHANISMS OF ACTION

The precise mechanism(s) by which zonisamide exerts its anticonvulsant effects is unknown. zonisamide may produce these effects through action at sodium and calcium channels. In vitro pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca2+ currents), consequently stabilizing neuronal membranes. Other in vitro studies have demonstrated that zonisamide (10–30 µg/mL) suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons) or neuronal or glial uptake of [3H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. zonisamide is a carbonic anhydrase inhibitor. The contribution of this pharmacological action to the therapeutic effects of zonisamide is unknown.

Dose & Administration

ADULTS

Administer Zonisade™ once or twice daily with or without food. The recommended initial dosage of Zonisade™ is 100 mg daily. The dosage may be increased by 100 mg daily every two weeks, based on clinical response and tolerability, to 400 mg daily. Patients who are tolerating Zonisade™ at 400 mg daily and require further reduction of seizures may be increased up to a maximum dosage of 600 mg daily. However, evidence from controlled trials shows no suggestion of increasing response above 400 mg/day.

PEDIATRICS

Pediatric patients 16 years and older-refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Avoid use of Zonisade™ in patients with renal failure (estimated GFR < 50 mL/min).

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral suspension: 100 mg/5 mL