ZONISADE®

(zonisamide oral suspension)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZONISADE® safely and effectively. See full prescribing information for ZONISADE®

ZONISADE (zonisamide oral suspension)
Initial U.S. Approval: 2000

-------------------------- INDICATIONS AND USAGE --------------------------

ZONISADE is indicated as adjunctive therapy for the treatment of partial-onset seizures in adults and pediatric patients 16 years of age and older (1).

---------------------- DOSAGE AND ADMINISTRATION ----------------------

- 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 (2.2).
- ZONISADE is given orally and can be taken with or without food (2.2).

--------------------- DOSAGE FORMS AND STRENGTHS ---------------------

ZONISADE: 100 mg/5 mL (3).

---------------------------- CONTRAINDICATIONS ----------------------------

ZONISADE is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide (4).

----------------------- WARNINGS AND PRECAUTIONS -----------------------

- Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias (5.1).
- Serious Skin Reactions: Discontinue ZONISADE at the first sign of rash unless clearly not drug related (5.2).
- Serious Hematologic Events: Aplastic anemia and agranulocytosis have been reported with zonisamide treatment (5.3).
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity: DRESS, also known as multiorgan hypersensitivity, has occurred with zonisamide (5.4).
- Oligohidrosis and Hyperthermia in Pediatric Patients: Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients (5.5).
- Acute Myopia and Secondary Angle Closure Glaucoma: If occurs, primary treatment is discontinuation of ZONISADE (5.6).
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior or ideation (5.7).
- Metabolic Acidosis: Baseline and periodic measurement of serum bicarbonate is recommended; consider dose reduction or discontinuation if appropriate (5.8).
- Seizures on Withdrawal of Antiepileptic Drugs: Withdraw ZONISADE gradually (5.9).
- 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 (5.10, 8.1, 8.3).

---------------------------- 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 (6).

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***.**

---------------------------- DRUG INTERACTIONS ----------------------------

- ZONISADE should be used with caution if used in combination with alcohol or other CNS depressants (7.1).
- 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 (7.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Assessments for Safety

To assess for metabolic acidosis, obtain baseline serum bicarbonate prior to initiating ZONISADE, and obtain periodic serum bicarbonate during treatment *[see Warnings and Precautions (5.8)]*.

2.2 Recommended Dosage

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 *[see Clinical Studies (14)].*

2.3 Important Administration Information

Shake well before every administration. To administer ZONISADE directly into the mouth, it is important that ZONISADE be measured with an accurate measuring device *[see Overdosage (10)]*. A household teaspoon is not an accurate measuring device. A pharmacist will provide an appropriate device and instructions for measuring the correct dose.

Administer ZONISADE orally with or without food.

Discard unused portion of ZONISADE 30 days after first opening the bottle.

2.4 Discontinuation of ZONISADE

When discontinuing ZONISADE, the dose should be decreased gradually. As with most antiepileptic drugs, avoid abrupt discontinuation, when possible, to minimize the risk of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.9)].*

3 DOSAGE FORMS AND STRENGTHS

Oral suspension: 100 mg/5 mL of zonisamide as a white to off-white, strawberry flavored liquid.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Potentially Fatal Reactions to Sulfonamides

Fatalities have occurred as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias [*see Warnings and Precautions (5.2, 5.3, 5.4)].* Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue ZONISADE immediately. Specific experience with sulfonamide-type adverse reaction to zonisamide is described below.

5.2 Serious Skin Reactions

Seven deaths from severe rash [i.e., Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)] were reported in the first 11 years of marketing in Japan. All of the patients were receiving other drugs in addition to zonisamide. In postmarketing experience from Japan, a total of 49 cases of SJS or TEN have been reported, a reporting rate of 46 per million patient-years of exposure. Although this rate is greater than background, it is probably an underestimate of the true incidence because of under-reporting. There were no confirmed cases of SJS or TEN in the US, European, or Japanese development programs.

In the US and European randomized controlled trials *[see Clinical Studies (14)]*, 6 of 269 (2.2%) patients who received zonisamide discontinued treatment because of rash compared to no patients who received placebo. Across all trials during the US and European development, rash that led to discontinuation of zonisamide was reported in 1.4% of patients (12.0 events per 1000 patient-years of exposure). During Japanese development, serious rash or rash that led to discontinuation of zonisamide was reported in 2.0% of patients (27.8 events per 1000 patient-years). Rash usually occurred early in treatment, with 85% reported within 16 weeks in the US and European studies and 90% reported within two weeks in the Japanese studies. There was no apparent relationship of dose to the occurrence of rash.

Discontinue ZONISADE at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of ZONISADE should not be resumed and alternative therapy should be considered.

5.3 Serious Hematologic Events

Two confirmed cases of aplastic anemia and one confirmed case of agranulocytosis were reported in the first 11 years of marketing in Japan, rates greater than generally accepted background rates. There were no cases of aplastic anemia and two confirmed cases of agranulocytosis in the US, European, or Japanese development programs. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

5.4 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, the active ingredient in ZONISADE. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident.

If such signs or symptoms are present, the patient should be evaluated immediately. ZONISADE should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.5 Oligohidrosis and Hyperthermia in Pediatric Patients

ZONISADE is not approved for use in patients below 16 years of age.

Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients.

During the pre-approval development program in Japan, one case of oligohidrosis was reported in 403 pediatric patients, an incidence of 1 case per 285 patient-years of exposure. While there were no cases reported in the US or European development programs, fewer than 100 pediatric patients participated in these trials.

In the first 11 years of marketing in Japan, 38 cases were reported, an estimated reporting rate of about 1 case per 10,000 patient-years of exposure. In the first year of marketing in the US, 2 cases were reported, an estimated reporting rate of about 12 cases per 10,000 patient-years of exposure. These rates are underestimates of the true incidence because of under-reporting. There has also been one report of heat stroke in an 18-year-old patient in the US.

Decreased sweating and an elevation in body temperature above normal characterized these cases. Many cases were reported after exposure to elevated environmental temperatures. Heat stroke, requiring hospitalization, was diagnosed in some cases.

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.

5.6 Acute Myopia and Secondary Angle Closure Glaucoma

Acute myopia and secondary angle closure glaucoma have been reported in patients receiving zonisamide, the active ingredient in ZONISADE. Elevated intraocular pressure can lead to serious sequelae, including permanent vision loss, if left untreated.

Symptoms in reported cases have included acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with ciliochoroidal effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within one month after initiating zonisamide therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with zonisamide has been reported both in pediatric patients and in adults. ZONISADE is not approved for use in patients below 16 years of age. The primary treatment to reverse symptoms is discontinuation of ZONISADE as rapidly as possible, according to the judgment of the treating physician. Other therapeutic measures, in conjunction with discontinuation of ZONISADE, may be helpful. Myopia and secondary angle closure glaucoma usually resolve or improve after discontinuation of zonisamide.

5.7 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.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing ZONISADE or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.8 Metabolic Acidosis

Zonisamide causes hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis). This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase. Generally, zonisamide-induced metabolic acidosis occurs early in treatment, but it can develop at any time during treatment. Metabolic acidosis generally appears dose-dependent and can occur at doses as low as 25 mg daily.

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.

Some manifestations of acute or chronic metabolic acidosis include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated, metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis. Nephrolithiasis has been observed in the clinical development program in 4% of adults treated with zonisamide, has also been detected by renal ultrasound in 8% of pediatric treated patients who had at least one ultrasound prospectively collected, and was reported as an adverse event in 3% (4/133) of pediatric patients *[see Warnings and Precautions (5.15)]*. Metabolic acidosis can also increase the risk for hyperammonemia, particularly in the presence of drugs which can cause hyperammonemia.

Chronic, untreated metabolic acidosis may result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fracture. Of potential relevance, zonisamide treatment was associated with reductions in serum phosphorus and increases in serum alkaline phosphatase, changes that may be related to metabolic acidosis and osteomalacia.

Chronic, untreated metabolic acidosis in pediatric patients may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of zonisamide on growth and bone-related sequelae has not been systematically investigated. ZONISADE is not approved for use in patients below 16 years of age.

Serum bicarbonate was not measured in the adjunctive controlled trials of adults with epilepsy. However, serum bicarbonate was studied in three clinical trials for indications which have not been approved: a placebo-controlled trial for migraine prophylaxis in adults, a controlled trial for monotherapy in epilepsy in adults, and an open label trial for adjunctive treatment of epilepsy in pediatric patients (3-16 years). In adults, mean serum bicarbonate reductions ranged from approximately 2 mEq/L at daily doses of 100 mg to nearly 4 mEq/L at daily doses of 300 mg. In pediatric patients, mean serum bicarbonate reductions ranged from approximately 2 mEq/L at daily doses from above 100 mg up to 300 mg, to nearly 4 mEq/L at daily doses from above 400 mg up to 600 mg.

In two controlled studies in adults, the incidence of a persistent treatment-emergent decrease in serum bicarbonate to less than 20 mEq/L (observed at 2 or more consecutive visits or the final visit) was dose-related at relatively low zonisamide doses. In the monotherapy trial of epilepsy, the incidence of a persistent treatment-emergent decrease in serum bicarbonate was 21% for daily zonisamide doses of 25 mg or 100 mg, and was 43% at a daily dose of 300 mg. In a placebo-controlled trial for prophylaxis of migraine, the incidence of a persistent treatment-emergent decrease in serum bicarbonate was 7% for placebo, 29% for 150 mg daily, and 34% for 300 mg daily. The incidence of persistent markedly abnormally low serum bicarbonate (decrease to less than 17 mEq/L and more than 5 mEq/L from a pretreatment value of at least 20 mEq/L) in these controlled trials was 2% or less.

In the pediatric study, the incidence of persistent, treatment-emergent decreases in serum bicarbonate to levels less than 20 mEq/L was 52% at doses up to 100 mg daily, was 90% for a wide range of doses up to 600 mg daily, and generally appeared to increase with higher doses. The incidence of a persistent markedly abnormally low serum bicarbonate value was 4% at doses up to 100 mg daily, was 18% for a wide range of doses up to 600 mg daily, and generally appeared to increase with higher doses. Some patients experienced moderately severe serum bicarbonate decrements down to a level as low as 10 mEq/L.

The relatively high frequencies of varying severities of metabolic acidosis observed in this study of pediatric patients (compared to the frequency and severity observed in various clinical trial development programs in adults) suggest that pediatric patients may be more likely to develop metabolic acidosis than adults.

Measurement of baseline and periodic serum bicarbonate during treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing ZONISADE (using dose tapering). If the decision is made to continue patients on ZONISADE in the face of persistent acidosis, alkali treatment should be considered.

5.9 Seizures on Withdrawal of Antiepileptic Drugs

As with most antiepileptic drugs, ZONISADE should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus *[see Dosage and Administration (2.3)]*. However, if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered. In these situations, appropriate monitoring is recommended.

5.10 Teratogenicity

Women of childbearing potential who are given ZONISADE should be advised to use effective contraception. Zonisamide produced fetal malformations in mice, rats, and dogs and was embryolethal in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects and embryofetal deaths, occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of zonisamide during pregnancy in humans may present a significant risk to the fetus *[see Use in Specific Populations (8.1)].*

Although human data to confirm findings in animals is limited, ZONISADE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

5.11 Cognitive/Neuropsychiatric Adverse Reactions

Use of zonisamide was frequently associated with central nervous system-related adverse reactions *[see Adverse Reactions (6.1)].* The most significant of these can be classified into three general categories: 1) psychiatric symptoms, including depression and psychosis, 2) cognitive dysfunction, and 3) somnolence or fatigue.

Psychiatric Symptoms

In placebo-controlled trials, 2.2% of patients discontinued zonisamide or were hospitalized for depression compared to 0.4% of placebo patients. Among all epilepsy patients treated with zonisamide, 1.4% were discontinued and 1.0% were hospitalized because of reported depression or suicide attempts. In placebo-controlled trials, 2.2% of patients discontinued zonisamide or were hospitalized because of psychosis or psychosis-related symptoms compared to no patients who received placebo. Among all epilepsy patients treated with zonisamide, 0.9% discontinued treatment and 1.4% were hospitalized because of reported psychosis or related symptoms.

Cognitive Dysfunction

Zonisamide, the active ingredient in ZONISADE, causes adverse reactions related to cognitive dysfunction (e.g., psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties). In placebo-controlled trials with zonisamide, psychomotor slowing and difficulty with concentration occurred in the first month of treatment and were associated with doses above 300 mg/day. Speech and language problems tended to occur after 6–10 weeks of treatment and at doses above 300 mg/day. Although in most cases these events were of mild to moderate severity, they at times led to withdrawal from treatment.

Somnolence and Fatigue

Somnolence and fatigue were frequently reported CNS adverse events during clinical trials with zonisamide. Although in most cases these events were of mild to moderate severity, they led to withdrawal from treatment in 0.2% of the patients enrolled in controlled trials. Somnolence and fatigue tended to occur within the first month of treatment. Somnolence and fatigue occurred most frequently at doses of 300–500 mg/day.

Risk Amelioration

Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of ZONISADE is known. Patients should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence and sedation, when ZONISADE is used with other drugs with sedative properties because of potential additive effects.

5.12 Hyperammonemia and Encephalopathy

Hyperammonemia and encephalopathy have been reported with the postmarketing use of zonisamide. Zonisamide, the active ingredient in ZONISADE, treatment inhibits carbonic anhydrase activity, which may cause metabolic acidosis that is associated with an increased risk for developing hyperammonemia. Hyperammonemia resulting from zonisamide can also be asymptomatic.

The risks of hyperammonemia and various manifestations of encephalopathy may be increased in patients treated with zonisamide and concomitantly taking other medications that can cause hyperammonemia, including valproic acid or topiramate *[see Warnings and Precautions (5)].* Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy and this risk may be increased by zonisamide use.

Measure serum ammonia concentration if signs or symptoms (e.g., unexplained change in mental status, vomiting, or lethargy) 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.

5.13 Kidney Stones

Zonisamide, the active ingredient in ZONISADE, may cause kidney stones. Among 991 patients treated during the development of zonisamide, 40 patients (4.0%) with epilepsy receiving zonisamide developed clinically possible or confirmed kidney stones (e.g., clinical symptomatology, sonography, etc.), at rate of 34 per 1000 patient-years of exposure (40 patients with 1168 years of exposure). Of these, 12 were symptomatic, and 28 were described as possible kidney stones based on sonographic detection. In nine patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonographic finding. The rate of occurrence of kidney stones was 28.7 per 1000 patient-years of exposure in the first six months, 62.6 per 1000 patient-years of exposure between 6 and 12 months, and 24.3 per 1000 patient-years of exposure after 12 months of use. There are no normative sonographic data available for either the general population or patients with epilepsy. Although the clinical significance of the sonographic findings may not be certain, the development of nephrolithiasis may be related to metabolic acidosis *[see Warnings and Precautions (5.8)].* The analyzed stones were composed of calcium or urate salts. In general, increasing fluid intake and urine output can help reduce the risk of stone formation, particularly in those with predisposing risk factors. It is unknown, however, whether these measures will reduce the risk of stone formation in patients treated with ZONISADE.

Although not approved in pediatric patients, sonographic findings consistent with nephrolithiasis were also detected in 8% of a subset of zonisamide treated pediatric patients who had at least one renal ultrasound prospectively performed in a clinical development program investigating open-label treatment. The incidence of kidney stone as an adverse event was 3% *[see Warnings and Precautions (5.8)].*

5.14 Effect on Renal Function

Zonisamide, the active ingredient in ZONISADE, can have an effect on renal function. In several clinical studies, zonisamide was associated with a statistically significant 8% mean increase from baseline of serum creatinine and blood urea nitrogen (BUN) compared to essentially no change in the placebo patients. The increase appeared to persist over time but was not progressive; this has been interpreted as an effect on glomerular filtration rate (GFR). There were no episodes of unexplained acute renal failure in clinical development in the US, Europe, or Japan. The decrease in GFR appeared within the first 4 weeks of treatment. In a 30-day study, the GFR returned to baseline within 2–3 weeks of drug discontinuation. There is no information about reversibility, after drug discontinuation, of the effects on GFR after long-term use. ZONISADE should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in the creatinine/BUN concentration. Avoid use of ZONISADE in patients with renal failure (estimated GFR < 50 mL/min) since there is insufficient experience concerning drug dosing and toxicity *[see Use in Specific Populations (8.6)]*. Consideration should be given to monitoring renal function periodically.

5.15 Status Epilepticus

Estimates of the incidence of treatment emergent status epilepticus in patients treated with zonisamide, the active ingredient in ZONISADE, are difficult because a standard definition was not employed. Nonetheless, in controlled trials, 1.1% of patients treated with zonisamide had an event labeled as status epilepticus compared to none of the patients treated with placebo. Among patients treated with zonisamide across all epilepsy studies (controlled and uncontrolled), 1.0% of patients had an event reported as status epilepticus.

6 ADVERSE REACTIONS

The following clinically signification adverse reactions are described elsewhere in the labeling:

- Potentially Fatal Reactions to Sulfonamides *[see Warnings and Precautions (5.1)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.2)]*
- Serious Hematologic Events *[see Warnings and Precautions (5.3)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity *[see Warnings and Precautions (5.4)]*
- Oligohidrosis and Hyperthermia in Pediatric Patients *[see Warnings and Precautions (5.5)]*
- Acute Myopia and Secondary Angle Closure Glaucoma *[see Warnings and Precautions (5.6)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.7)]*
- Metabolic Acidosis *[see Warnings and Precautions (5.8)]*
- Seizures on Withdrawal of Antiepileptic Drugs *[see Warnings and Precautions (5.9)]*
- Teratogenicity *[see Warnings and Precautions (5.10)]*
- Cognitive/Neuropsychiatric Adverse Reactions *[see Warnings and Precautions (5.11)]*
- Hyperammonemia and Encephalopathy *[see Warnings and Precautions (5.12)]*
- Kidney Stones *[see Warnings and Precautions (5.13)]*
- Effect on Renal Function *[see Warnings and Precautions (5.14)]*
- Status Epilepticus *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Placebo-Controlled Trials with Zonisamide Capsules *[see Clinical Studies (14)]*

The most common adverse reactions with zonisamide capsules (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.

In controlled clinical trials, 12% of patients receiving zonisamide as adjunctive therapy discontinued because of an adverse reaction compared to 6% receiving placebo. Approximately 21% of the 1,336 patients with epilepsy who received zonisamide in clinical studies discontinued treatment because of an adverse reaction. The most common adverse reactions leading to discontinuation were somnolence, fatigue and/or ataxia (6%), anorexia (3%), difficulty concentrating (2%), difficulty with memory, mental slowing, nausea/vomiting (2%), and weight loss (1%). Many of these adverse reactions were dose-related *[see Warnings and Precautions (5)].*

Table 2 lists adverse reactions that occurred in at least 2% of patients treated with zonisamide capsules in controlled clinical trials that were numerically more common in the zonisamide group. In these studies, either zonisamide or placebo was added to the patient's current AED therapy.

Table 2. Adverse Reactions that Occurred in at least 2% of Patients Treated with Zonisamide Capsules and More Frequently than in Patients who Received Placebo in Placebo-Controlled, Adjunctive Trials

BODY SYSTEM/Adverse Reaction	Zonisamide Capsules (n=269) %	Placebo (n=230) %
BODY AS A WHOLE		
Headache	10	8
Abdominal Pain	6	3
Flu Syndrome	4	3
DIGESTIVE		
Anorexia	13	6
Nausea	9	6
Diarrhea	5	2
Dyspepsia	3	1
Constipation	2	1
Dry Mouth	2	1
HEMATOLOGIC AND LYMPHATIC		
Ecchymosis	2	1
METABOLIC AND NUTRITIONAL		
Weight Loss	3	2
NERVOUS SYSTEM		
Dizziness	13	7
Ataxia	6	1
Nystagmus	4	2
Paresthesia	4	1
NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-ALTERED COGNITIVE FUNCTION		
Confusion	6	3
Difficulty Concentrating	6	2
Difficulty with Memory	6	2
Mental Slowing	4	2
NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (NON-PSYCHOSIS-RELATED)		
Agitation/Irritability	9	4
Depression	6	3
Insomnia	6	3
Anxiety	3	2
Nervousness	2	1
NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (PSYCHOSIS-RELATED)		
Schizophrenic/Schizophreniform Behavior	2	0
NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-CNS DEPRESSION		
Somnolence	17	7
Fatigue	8	6
Tiredness	7	5
NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-SPEECH AND LANGUAGE ABNORMALITIES		
Speech Abnormalities	5	2
Difficulties in Verbal Expression	2	<1
RESPIRATORY		
Rhinitis	2	1
SKIN AND APPENDAGES		
Rash	3	2
SPECIAL SENSES		
Diplopia	6	3
Taste Perversion	2	0

Laboratory Tests

Zonisamide increases serum chloride and alkaline phosphatase and decreases serum bicarbonate *[see Warnings and Precautions (5.8)]*, phosphorus, calcium, and albumin.

Other Adverse Reactions in Clinical Trials of Zonisamide Capsules

Zonisamide capsules have been administered to 1,598 individuals during all clinical trials, only some of which were placebo-controlled. The frequencies represent the proportion of the 1,598 individuals exposed to zonisamide capsules who experienced an event on at least one occasion. All events are included except those already listed in the previous table or discussed in *[see Warnings and Precautions (5)]*, trivial events, those too general to be informative, and those not reasonably associated with zonisamide.

Events are further classified within each category and listed in order of decreasing frequency as follows: frequent occurring in at least 1:100 patients; infrequent occurring in 1:100 to 1:1000 patients; rare occurring in fewer than 1:1000 patients.

Body as a Whole: *Frequent:* Accidental injury, asthenia. *Infrequent:* Chest pain, flank pain, malaise, allergic reaction, face edema, neck rigidity. *Rare:* Lupus erythematosus.

Cardiovascular: *Infrequent:* Palpitation, tachycardia, vascular insufficiency, hypotension, hypertension, thrombophlebitis, syncope, bradycardia. *Rare:* Atrial fibrillation, heart failure, pulmonary embolus, ventricular extrasystoles.

Digestive: *Frequent:* Vomiting. *Infrequent:* Flatulence, gingivitis, gum hyperplasia, gastritis, gastroenteritis, stomatitis, cholelithiasis, glossitis, melena, rectal hemorrhage, ulcerative stomatitis, gastro-duodenal ulcer, dysphagia, gum hemorrhage. *Rare:* Cholangitis, hematemesis, cholecystitis, cholestatic jaundice, colitis, duodenitis, esophagitis, fecal incontinence, mouth ulceration.

Hematologic and Lymphatic: *Infrequent:* Leukopenia, anemia, immunodeficiency, lymphadenopathy. *Rare:* Thrombocytopenia, microcytic anemia, petechia.

Metabolic and Nutritional: *Infrequent:* Peripheral edema, weight gain, edema, thirst, dehydration. *Rare:* Hypoglycemia, hyponatremia, lactic dehydrogenase increased, SGOT increased, SGPT increased.

Musculoskeletal: *Infrequent:* Leg cramps, myalgia, myasthenia, arthralgia, arthritis.

Nervous System: *Frequent:* Tremor, convulsion, abnormal gait, hyperesthesia, incoordination. *Infrequent:* Hypertonia, twitching, abnormal dreams, vertigo, libido decreased, neuropathy, hyperkinesia, movement disorder, dysarthria, cerebrovascular accident, hypotonia, peripheral neuritis, reflexes increased. *Rare:* Dyskinesia, dystonia, encephalopathy, facial paralysis, hypokinesia, hyperesthesia, myoclonus, oculogyric crisis.

Behavioral Abnormalities –Non-Psychosis-Related: *Infrequent:* Euphoria.

Respiratory: *Frequent:* Pharyngitis, cough increased. *Infrequent*: Dyspnea. *Rare:* Apnea, hemoptysis.

Skin and Appendages: *Frequent:* Pruritus. *Infrequent:* Maculopapular rash, acne, alopecia, dry skin, sweating, eczema, urticaria, hirsutism, pustular rash, vesiculobullous rash.

Special Senses: *Frequent:* Amblyopia, tinnitus. *Infrequent:* Conjunctivitis, parosmia, deafness, visual field defect, glaucoma. *Rare:* Photophobia, iritis.

Urogenital: *Infrequent:* Urinary frequency, dysuria, urinary incontinence, hematuria, impotence, urinary retention, urinary urgency, amenorrhea, polyuria, nocturia. *Rare:* Albuminuria, enuresis, bladder pain, bladder calculus, gynecomastia, mastitis, menorrhagia.

6.2 Postmarketing Experience

The following serious adverse reactions have been reported since approval and use of zonisamide worldwide. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure.

Acute pancreatitis, rhabdomyolysis, increased creatine phosphokinase, and drug reaction with eosinophilia and systemic symptoms (DRESS), acute myopia and secondary angle closure glaucoma, and hyperammonemia and encephalopathy *[see Warnings and Precautions (5)].*

7 DRUG INTERACTIONS

7.1 CNS Depressants

Concomitant use of ZONISADE with other CNS depressants, including alcohol, may increase the risk of CNS depression, as well as other cognitive and/or neuropsychiatric adverse events *[see Warnings and Precautions (5.11)].*

7.2 Other Carbonic Anhydrase Inhibitors

Concomitant use of ZONISADE, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor, may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation *[see Warnings and Precautions (5.8, 5.15)].* Therefore, if ZONISADE is given concomitantly with another carbonic anhydrase inhibitor, monitor the patient for the appearance or worsening of metabolic acidosis *[see Clinical Pharmacology (12.1, 12.3)].*

7.3 CYP3A4 Inducers

If co-administration with a potent CYP3A4 inducer is necessary, the patient should be closely monitored and the dose of ZONISAMIDE and other drugs that CYP3A4 substrates may need to be adjusted *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs, such as ZONISADE, during pregnancy. To provide information regarding the effects of in utero exposure to ZONISADE, physicians are advised to recommend that pregnant patients taking ZONISADE enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334 and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Risk Summary

Based on findings from animal studies, ZONISADE may cause fetal harm when administered to a pregnant woman. Zonisamide causes metabolic acidosis in humans *[see Warnings and Precautions (5.8)]*. There are no reports of metabolic acidosis with use of zonisamide in pregnancy; however, there are published prospective cohort studies that suggest an increased rate of small for gestational age infants in pregnancies exposed to zonisamide, which may be associated with metabolic acidosis *(see Clinical Considerations and Data).*

The available published data from the NAAED Pregnancy Registry has not identified a drug-associated risk of major birth defects with zonisamide use in pregnancy. Although a small prospective cohort study reported an increased risk of major birth defects in zonisamide-exposed pregnancies, this study has methodologic limitations, including small sample size and inability to account for potential confounders *(see Data).* The available published data pertaining to the use of zonisamide during pregnancy are insufficient to evaluate for a drug-associated risk of miscarriage.

In animal studies, administration of zonisamide during pregnancy produced fetal malformations in multiple species and embryofetal (monkey) or perinatal (rat) death at maternal plasma levels similar to or lower than therapeutic levels in humans *[see Warnings and Precautions (5.10) and Data].*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the general U.S. population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Dose Adjustments During Pregnancy and the Postpartum Period

As with other AEDs, physiological changes during pregnancy may affect zonisamide concentrations and/or therapeutic effect. There have been reports of decreased zonisamide concentrations during pregnancy and restoration of pre-pregnancy concentrations after delivery. Dose adjustments may be necessary to maintain clinical response.

Maternal Adverse Reactions

Metabolic acidosis in pregnancy (due to other causes) may be associated with decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor. There are no reports of metabolic acidosis or fetal death with use of zonisamide in pregnancy *[see Warnings and Precautions (5.8)].*

Fetal/Neonatal Adverse Reactions

Newborns of mothers treated with zonisamide should be monitored for metabolic acidosis because of transfer of zonisamide to the fetus and possible occurrence of transient metabolic acidosis following birth. Transient metabolic acidosis has been reported in neonates born to mothers treated during pregnancy with a different carbonic anhydrase inhibitor.

Data

Human Data

A prospective cohort study from the NAAED Pregnancy Registry has not identified an increase in the rate of major birth defects (1.4%) in over 200 first trimester pregnancies exposed to zonisamide monotherapy use. Methodological limitations include small sample size and selection bias.

A prospective cohort study from the United Kingdom and Ireland Epilepsy Pregnancy Registry (UKIEPR) reported an increased rate of major birth defects (13%) in 26 first trimester pregnancies exposed to zonisamide monotherapy use. Methodological limitations include small sample size and inability to account for potential confounders.

Prospective cohort studies, including data from NAAED Pregnancy Registry and UKIEPR, have reported increased rates of small for gestational age infants in those exposed to zonisamide during pregnancy compared to lamotrigine-exposed pregnancies and the unexposed general population.

Animal Data

In mice, treatment of pregnant animals with zonisamide (0, 125, 250, or 500 mg/kg/day) during the period of organogenesis resulted in increased incidences of fetal malformations (skeletal and/or craniofacial defects) at all doses tested. A no-effect dose for adverse effects on embryofetal development in mice was not identified. The lowest dose tested was approximately 1.5 times that in humans at the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m² basis.

In rats, an increased frequency of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, decreased skeletal ossification) was observed in the offspring of dams treated with zonisamide (0, 20, 60, or 200 mg/kg/day) throughout organogenesis at all doses. A no-effect dose for adverse effects on embryofetal development in rats was not identified. The lowest dose tested was approximately 0.5 times the MRHD on a mg/m² basis.

Following administration of zonisamide (0, 10, 30, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular malformations (ventricular septal defects, cardiomegaly, various valvular and arterial anomalies) were found at doses of 30 mg/kg/day or greater. Cardiovascular malformations were found in approximately 50% of all fetuses exposed to the high dose. Incidences of skeletal malformations were also increased at the high dose, and fetal growth retardation and increased frequencies of skeletal variations were seen at all doses. Plasma levels in pregnant dogs (12 µg/mL) at the low and mid doses tested (10 and 30 mg/kg, respectively) were lower than those in humans at the MRHD; plasma levels at the high dose tested in pregnant dogs were similar to those in humans at the MRHD.

In cynomolgus monkeys, administration of zonisamide (0, 10 or 20 mg/kg/day) to pregnant animals during organogenesis resulted in embryofetal deaths at both doses. The possibility that these deaths were due to malformations cannot be ruled out. A no-effect dose for embryofetal death was not identified. At the low dose tested, peak plasma levels in pregnant monkey were substantially lower than that in humans at the MRHD.

Perinatal death was increased among the offspring of rats treated with zonisamide (0, 10, 30, or 60mg/kg/day) from the latter part of gestation up to weaning at the high dose. The no-effect dose (30 mg/kg/day) for adverse peri- and postnatal developmental effects in rats is less than the MRHD on a body surface area (mg/m²) basis.

8.2 Lactation

Risk Summary

Zonisamide is readily transferred to human milk, with a reported milk-to-plasma ratio ranging between 0.7 to 0.9 in the published lactation studies. There are no published reports of adverse effects on the breastfed infant exposed to zonisamide during breastfeeding. There are no data on the effect of zonisamide on milk production. Because ZONISADE has been associated with metabolic acidosis in adult and pediatric patients and hyperthermia in pediatric patients, infants exposed to ZONISADE during breastfeeding should be monitored for poor feeding, weight loss, excess sedation, decreased muscle tone, and elevated temperature *[see Warnings and Precautions (5.8)]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZONISADE and any potential adverse effects on the breastfed infant from ZONISADE or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on animal data, zonisamide can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.10)]*. Advise females of reproductive potential to use effective contraception during treatment with ZONISADE and for one month after discontinuation.

Infertility

Females

Based on findings from animal fertility studies, ZONISADE may impair fertility in females *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of ZONISADE have been established in patients 16 years of age and older by evidence from adequate and well-controlled studies of zonisamide *[see Clinical Studies (14)]*.

Safety and effectiveness in pediatric patients below the age of 16 have not been established. Acute myopia and secondary angle closure glaucoma have been reported in pediatric patients *[see Warnings and Precautions (5.6)]*. Cases of oligohidrosis and hyperpyrexia have been reported *[see Warnings and Precautions (5.5)]*. Zonisamide commonly causes metabolic acidosis in pediatric patients *[see Warnings and Precautions (5.8)]*. Chronic untreated metabolic acidosis in pediatric patients may cause nephrolithiasis and/or nephrocalcinosis, osteoporosis and/or osteomalacia (potentially resulting in rickets), and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of zonisamide on growth and bone-related sequelae has not been systematically investigated.

8.5 Geriatric Use

Single dose pharmacokinetic parameters are similar in elderly and young healthy volunteers *[see Clinical Pharmacology (12.3)]*. Clinical studies of zonisamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

ZONISADE is cleared via renal pathway *[see Clinical Pharmacology (12.3)]*. Patients with renal impairment might require slower titration, and more frequent monitoring is required. Avoid use of ZONISADE in patients with renal failure (estimated GFR < 50 mL/min). ZONISADE should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in the creatinine/BUN concentration *[see Warnings and Precautions (5.14)]*.

10 OVERDOSAGE

10.1 Human Experience

During zonisamide clinical development, three patients ingested unknown amounts of zonisamide as suicide attempts, and all three were hospitalized with CNS symptoms. One patient became comatose and developed bradycardia, hypotension, and respiratory depression; the zonisamide plasma level was 100.1 µg/mL measured 31 hours post-ingestion. Zonisamide plasma levels fell with a half-life of 57 hours, and the patient became alert five days later.

10.2 Management

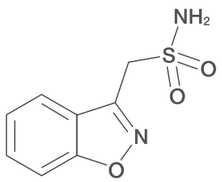
No specific antidotes for zonisamide overdosage are available. Following a suspected recent overdose, emesis should be induced or gastric lavage performed with the usual precautions to protect the airway. General supportive care is indicated, including frequent monitoring of vital signs and close observation.

Zonisamide has a long half-life *[see Clinical Pharmacology (12.3)]*. Due to the low protein binding of zonisamide (40%), renal dialysis may be effective. The effectiveness of renal dialysis as a treatment of overdose has not been formally studied. A poison control center should be contacted for information on the management of ZONISADE overdosage.

11 DESCRIPTION

ZONISADE (zonisamide oral suspension) is chemically classified as a sulfonamide. The active ingredient is zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. The empirical formula is $C_8H_8N_2O_3S$ with a molecular weight of 212.23. Zonisamide is a white powder, pKa = 10.2, and is moderately soluble in water (0.80 mg/mL) and 0.1 N HCl (0.50 mg/mL).

The chemical structure is:



ZONISADE is an aqueous white to off-white liquid oral suspension. Each mL contains 20 mg of zonisamide. Inactive ingredients include carboxymethylcellulose sodium, citric acid monohydrate, microcrystalline cellulose, purified water, sodium benzoate, strawberry flavor, sucralose, trisodium citrate dihydrate, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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 Ca^{2+} 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 [^{3}H]-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.

12.2 Pharmacodynamics

As a carbonic anhydrase inhibitor, ZONISADE may cause metabolic acidosis and may also increase the risks of hyperammonemia and kidney stone formation *[see Warnings and Precautions (5.8, 5.13, 5.15) and Drug Interactions (7.2)]*.

12.3 Pharmacokinetics

Absorption

Following a 100 mg ZONISADE dose in normal volunteers, the time to maximum plasma concentrations (T_{max}) occurred within 0.5–5 hours.

Zonisamide pharmacokinetics are dose-proportional in the range of 200 to 400 mg. Once a stable dose is reached, steady state is achieved within 14 days.

Effect of Food

When ZONISADE is administered with food, the zonisamide T_{max} is delayed, occurring at 3.5–7.5 hours, but food has no effect on the bioavailability of zonisamide.

Distribution

The apparent volume of distribution (V/F) of zonisamide is about 1.45 L/kg following a 400 mg oral dose. Zonisamide, at concentrations of 1.0–7.0 mcg/mL, is approximately 40% bound to human plasma proteins. Zonisamide extensively binds to erythrocytes, resulting in an eight-fold higher concentration of zonisamide in red blood cells than in plasma. Protein binding of zonisamide is unaffected in the presence of therapeutic concentrations of phenytoin, phenobarbital, or carbamazepine.

Elimination

The plasma clearance of oral zonisamide is approximately 0.30–0.35 mL/min/kg in patients not receiving enzyme-inducing antiepileptic drugs (AEDs). The clearance of zonisamide is increased to 0.5 mL/min/kg in patients concurrently on enzyme-inducing AEDs *(see Potential for Other Drugs to Affect ZONISADE)*. After a single-dose administration, renal clearance of zonisamide is approximately 3.5 mL/min.

Metabolism

Zonisamide is metabolized by N-acetyl-transferases to form N-acetyl zonisamide and by CYP3A4 to form 2–sulfamoylacetylphenol (SMAP).

Excretion

The elimination half-life of zonisamide in plasma is approximately 63 hours. The elimination half-life of zonisamide in red blood cells is approximately 105 hours. Zonisamide is excreted primarily in urine as parent drug and as the glucuronide of a metabolite. Following multiple dosing, 62% of the radiolabeled dose was recovered in the urine, with 3% in the feces by day 10. Of the excreted dose, 35% was recovered as zonisamide, 15% as N-acetyl zonisamide, and 50% as the glucuronide of SMAP.

Specific Populations

Patients with Renal Impairment

Single 300 mg zonisamide doses were administered to three groups of volunteers. Group 1 was a healthy group with a creatinine clearance ranging from 70–152 mL/min. Group 2 and Group 3 had creatinine clearances ranging from 14.5–59 mL/min and 10–20 mL/min, respectively. Zonisamide renal clearance decreased with decreasing renal function (3.42, 2.50, and 2.23 mL/min, respectively). Marked renal impairment (creatinine clearance < 20 mL/min) was associated with an increase in zonisamide AUC of 35% *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

The pharmacokinetics of zonisamide in patients with impaired liver function have not been studied.

Age

The pharmacokinetics of a 300 mg single dose of zonisamide were similar in young (mean age 28 years) and elderly subjects (mean age 69 years).

Drug Interaction Studies

In-Vitro Studies

Enzymes

In vitro studies using human liver microsomes show insignificant (<25%) inhibition of cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4, 2B6, or 2C8 at zonisamide levels approximately two-fold or greater than clinically relevant unbound serum concentrations. Therefore, ZONISADE is not expected to affect the pharmacokinetics of other drugs via cytochrome P450-mediated mechanisms.

Transporters

An *in-vitro* study showed that zonisamide is a weak inhibitor of P-gp (MDR1).

In-Vivo Studies

Potential for Zonisamide to Affect Other Drugs

Antiepileptic Drugs

In epileptic patients, steady state dosing with zonisamide capsules resulted in no clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, or sodium valproate.

Oral Contraceptives

In healthy subjects, steady state dosing with zonisamide capsules did not affect serum concentrations of ethinylestradiol or norethisterone in a combined oral contraceptive.

CYP2D6 Substrates

Coadministration of multiple dosing of zonisamide up to 400 mg/day with single 50-mg doses of desipramine did not significantly affect the pharmacokinetic parameters of desipramine, a probe drug for CYP2D6 activity.

Potential for Other Drugs to Affect ZONISADE

CYP3A4 Inducers

The half-life of zonisamide following a 400 mg dose in patients concurrently on enzyme-inducing AEDs such as phenytoin, carbamazepine, or phenobarbital, was between 27-38 hours; the half-life of zonisamide in patients concurrently on the non-enzyme inducing AED, valproate, was 46 hours.

These effects are unlikely to be of clinical significance when ZONISADE is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4 inducing antiepileptic or other drugs are withdrawn, dose adjusted or introduced, an adjustment of the ZONISADE dose may be required *[see Drug Interactions (7.3)]*.

CYP3A4 Inhibitors

Steady-state dosing of either ketoconazole (400 mg/day) or cimetidine (1200 mg/day) had no clinically relevant effects on the single dose pharmacokinetics of zonisamide given to healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

Carcinogenicity

No evidence of carcinogenicity was found in mice or rats following dietary administration of zonisamide for two years at doses of up to 80 mg/kg/day. In mice, this dose is approximately equivalent to the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m^2 basis. In rats, this dose is 1–2 times the MRHD on a mg/m^2 basis.

Mutagenesis

Zonisamide was mutagenic in an in vitro chromosomal aberration assay in CHL cells. Zonisamide was not mutagenic or clastogenic in other in vitro assays (Ames, mouse lymphoma tk assay, chromosomal aberration in human lymphocytes) or in the in vivo rat bone marrow cytogenetics assay.

Impairment of Fertility

Rats treated with zonisamide (20, 60, or 200 mg/kg) before mating and during the initial gestation phase showed signs of reproductive toxicity (decreased corpora lutea, implantations, and live fetuses) at all doses. The low dose in this study is approximately 0.5 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.

14 CLINICAL STUDIES

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 multicenter, 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 antiepilepsy 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 3. Median % Reduction in All Partial-Onset Seizures and % Responders in Primary Efficacy Analyses: Intent-To-Treat Analysis

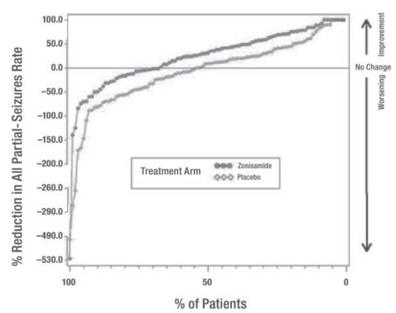
Study	Median % Reduction in Partial-Onset Seizures		% Responders	
	Zonisamide Capsules	Placebo	Zonisamide Capsules	Placebo
Study 1:	n=98	n=72	n=98	n=72
Weeks 8-12:	40.5%*	9.0%	41.8%*	22.2%
Study 2:	n=69	n=72	n=69	n=72
Weeks 5-12:	29.6%*	-3.2%	29.0%	15.0%
Study 3:	n=67	n=66	n=67	n=66
Weeks 5-12:	27.2%*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

Table 4. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZONISADE (zonisamide oral suspension) is a white to off-white, strawberry flavored liquid containing 100 mg/5 mL zonisamide. It is supplied in a 150 mL amber colored PET bottle with a child resistant cap.

NDC Number: 52652-8001-1

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light.

Discard unused portion of ZONISADE 30 days after first opening of the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration

Inform patients that a pharmacist will provide an appropriate device and instructions for measuring the correct dose and that a household teaspoon is not an accurate measuring device. Instruct patients to shake ZONISADE well and discard any unused portion after 30 days of opening the bottle *[see Dosage and Administration (2.2)]*.

Drowsiness

ZONISADE may produce drowsiness, especially at higher doses. Patients should be advised not to drive a car or operate other complex machinery until they have gained experience on ZONISADE sufficient to determine whether it affects their performance. Because of the potential of zonisamide to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, ZONISADE should be used with caution if used in combination with alcohol or other CNS depressants.

Serious Skin Reactions

Patients should contact their physicians immediately if a skin rash develops *[see Warnings and Precautions (5.2)]*.

Acute Myopia and Secondary Angle Closure Glaucoma

Instruct patients to seek immediate medical attention if they experience blurred vision, visual disturbances, or periorbital pain *[see Warnings and Precautions (5.6)]*.

Kidney Stones

Patients should contact their physician immediately if they develop signs or symptoms, such as sudden back pain, abdominal pain, and/or blood in the urine, that could indicate a kidney stone. Increasing fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for stones *[see Warnings and Precautions (5.15)]*.

Oligohidrosis and Hyperthermia in Pediatric Patients

Patients should contact their physician immediately if a child has been taking ZONISADE and is not sweating as usual with or without a fever *[see Warnings and Precautions (5.5)]*.

Serious Hematologic Events

Because zonisamide can cause hematological complications, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising *[see Warnings and Precautions (5.3)]*.

Suicidal Behavior and Ideation

Counsel patients and caregivers that AEDs, including ZONISADE, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers *[see Warnings and Precautions (5.7)]*.

Hyperammonemia and Encephalopathy

Warn patients about the possible development of hyperammonemia with or without encephalopathy. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy and/or vomiting. Instruct patients to contact their physician if they develop unexplained lethargy, vomiting, or changes in mental status *[see Warnings and Precautions (5.13)]*.

Metabolic Acidosis

Patients should contact their physician immediately if they develop fast breathing, fatigue/tiredness, loss of appetite, or irregular heartbeat or palpitations, which are possible manifestations of metabolic acidosis *[see Warnings and Precautions (5.8)]*.

Pregnancy

Advise pregnant women and females of reproductive potential of the risk to a fetus. Advise pregnant women to inform their healthcare provider of a known or suspected pregnancy.

Advise women who are exposed to ZONISADE during pregnancy that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to ZONISADE during pregnancy. Encourage patients to report their pregnancy to North American Antiepileptic Drug (NAAED) Pregnancy Registry at 1-888-233-2334 or http://www.aedpregnancyregistry.org/ *[see Use in Specific Populations (8.1)]*.

Lactation

Advise breastfeeding women using ZONISADE to monitor infants for increased sleepiness, decreased appetite, and elevated temperature and to seek medical attention if they notice these signs *[see Use in Specific Populations (8.2)]*.

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This product's labeling may have been updated. For current Full Prescribing Information, please visit www.zonisade.com

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