Zonisamide USP is an antiepileptic drug classified as a sulfonamide and unrelated to other antiepileptic agents. The active ingredient is zonisamide USP, 1,2-benzisoxazole-3-methanesulfonamide. The empirical formula is C9H8N2O3S with a molecular weight of 212.23. Zonisamide USP is a white powder, pKa = 10.2, and is moderately soluble in water (0.60 mg/mL) and 0.1 N HCl (0.20 mg/mL).

The chemical structure is:

Zonisamide is supplied for oral administration as capsules containing 100 mg zonisamide USP. Each capsule contains the labeled amount of zonisamide USP plus the following inactive ingredients: microcrystalline cellulose, hypromellose, vegetable oil, gelatin and colors. Component of gelatin capsules (For 100 mg: titanium dioxide, gelatin and FDA E172 red iron oxide). Imprim ink dyer (Black SW-9008/SW-9009).

**CLINICAL PHARMACOLOGY**

**Mechanism of Action:**
The precise mechanism(s) by which zonisamide exerts its antiepileptic effect is unknown. Zonisamide demonstrated anticonvulsant activity in several experimental models. In animals, zonisamide was effective against tonic and clonic seizures induced by maximal electroshock but ineffective against clonic seizures induced by subcutaneous pentyleneetrazen. Zonisamide raised the threshold for generalized seizures in the kindled rat model and reduced the duration of cortical focal seizures induced by electrical stimulation of the visual cortex in cats. Furthermore, zonisamide suppressed both interictal spikes and the secondarily generalized seizures produced by cortical application of tonic acid gel in rats or by cortical freezing in cats. The relevance of these models to man is unknown.

Zonisamide may produce these effects through actions 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), consequent stabilizing neuronal membranes and suppressing neuronal hypersynchronization. In vitro binding studies have demonstrated that zonisamide binds to the GABA receptors/tocaine receptor homolog complexes in an allosteric fashion which does not produce changes in chloride flux. Other in vitro studies have demonstrated that zonisamide (10 to 30 mcg/mL) suppresses synaptic-driven electrical activity without affecting postsynaptic GABA or glutamate responses (altered mouse spinal cord neurons) or neuronal or glial uptake of [3H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to influence the synaptic activity of GABA. In vivo microdialysis studies demonstrated that zonisamide facilitates both dopaminergic and serotonergic neurotransmission.

Zonisamide is a carbonic anhydrase inhibitor. The contribution of this pharmacological action to the antiepileptic effects of zonisamide is unknown. However, as a carbonic anhydrase inhibitor, zonisamide may cause metabolic acidosis (see WARNINGS, Metabolic Acidosis subsection).

**Pharmacokinetics:**
Following a 200 to 400 mg oral zonisamide dose, peak plasma concentrations (range: 2-5 mcg/mL) in normal volunteers occur within 2 to 6 hours. In the presence of food, the time to maximum concentration is delayed, occurring at 4 to 6 hours, but food has no effect on the bioavailability of zonisamide. Zonisamide extensively binds to erythrocytes, resulting in an eight-fold higher concentration of zonisamide in red blood cells (RBC) than in plasma. The pharmacokinetics of zonisamide are dose proportional in the range of 200 to 400 mg, but the Vₘₐₓ and AUC increase disproportionately at 800 mg, perhaps due to saturable binding of zonisamide to RBC. Once a stable dose is reached, steady state is achieved within 14 days. The elimination half-life of zonisamide in plasma is about 63 hours. The elimination half-life of zonisamide in RBC is approximately 105 hours.

The apparent volume of distribution (Vₐ) of zonisamide is about 1.45 L/kg following a 400 mg oral dose. Zonisamide, at concentrations of 1.0 to 7.0 mcg/mL, is approximately 40% bound to human plasma proteins. Protein binding of zonisamide is unaffected in the presence of therapeutic concentrations of phenytoin, phenobarbital or carbamazepine.

**Metabolism and Excretion:**
Following oral administration of 14C-zonisamide to healthy volunteers, only zonisamide was detected in plasma. Zonisamide is excreted primarily in the urine as parent drug and as the glucuronide of a metabolite. Following multiple dosing, 62% of the 14C-dose was recovered in the urine, with 8% in the feces by day 10. Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction to form the open ring metabolite, 2-acetylaminoacetamide (SMAP). Of the excreted dose, 35% was recovered as zonisamide, 15% as N-acetyl zonisamide, and 50% as the glucuronide of SMAP. Reduction of zonisamide to SMAP is mediated by cytochrome P450 isozyme 3A4 (CYP3A4). Zonisamide does not induce its own metabolism. Plasma clearance of zonisamide is approximately 0.30 to 0.35 mL/min in patients not receiving enzyme-inhibiting antiepileptic drugs (AEDs). The clearance of zonisamide is increased to 0.5 to 1.0 mL/min in patients concurrently co-enzyme-inhibiting AEDs.

Renal clearance is about 3.5 mL/min. The clearance of an oral dose of zonisamide from RBC is 2 mL/min.

**Special Populations:**

**Renal Insufficiency:** 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 to 152 mL/min. Group 2 and Group 3 had creatinine clearances ranging from 14.5 to 59 mL/min and 10 to 20 mL/min, respectively. Zonisamide renal clearance decreased with decreasing renal function (342, 250, 221 mL/min, respectively). Marked renal impairment (creatinine clearance < 20 mL/min) was associated with an increase in zonisamide AUC of 35% (see WARNINGS, Metabolic Acidosis subsection).

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

**Gender and Race:** Information on the effect of gender and race on the pharmacokinetics of zonisamide is not available.

**Interactions of Zonisamide with Other Antiepilepsy Drugs (AEDs):**
Concomitant medication with drugs that either induce or inhibit CYP3A4 may alter serum concentrations of zonisamide. Concomitant administration of phenytoin and carbamazepine increases zonisamide plasma clearance from 30.3 to 35.5 mL/min to 35.5 to 3.5 mL/min. The half-life of zonisamide is decreased to 27 hours by phenytoin, to 38 hours by phenobarbital and carbamazepine, and to 46 hours by valproate. Plasma protein binding of phenytoin and carbamazepine was not affected by zonisamide (see PRECAUTIONS, Drug Interactions subsection).

**Interactions of Zonisamide with Other Carbonic Anhydrase Inhibitors:**
Concomitant use of zonisamide as a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., trimethoprim, acetazolamide or dapsone), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if zonisamide is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis (see PRECAUTIONS, Drug Interactions subsection).

**Clinical Studies:**
The effectiveness of zonisamide as adjunctive therapy (added to other antiepilepsy drugs) has been established in three multicenter, placebo-controlled, double-blind, 3-month clinical trials (two domestic, one European). In 495 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 despite receiving one or two antiepilepsy drugs at therapeutic concentrations. One group (200 mg/d) experienced a 30% or greater seizure reduction from baseline frequency. The secondary measure was proportion of patients achieving a 50% or greater seizure reduction from baseline (response). 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 4-month baseline observation period, then received placebo or zonisamide in one of two dose escalation regimens; either 100 mg/day for five weeks, 200 mg/day for one week, 300 mg/day for one week, and 400 mg/day for five weeks; or 100 mg/day for five weeks, then 200 mg/day for one week, then 300 mg/day for one week, then 400 mg/day for five weeks.
rate was consistently higher for the zonisamide groups compared to the placebo groups. For example, the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure rate. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of decrease in seizure rate), while a negative value indicates a worsening from baseline (i.e., an increase in seizure rate). Analysis of the data (first 4 weeks) during titration demonstrated statistically significant differences favoring zonisamide for all partial seizure rate was at least as great as that indicated on the Y-axis in the second and third placebo-controlled trials. 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,

Table 1: Median % Reduction in All Partial Seizures and % Responders in Primary Efficacy Analyses: Intact-1 to-Treatment Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Median % Reduction in Partial Seizures</th>
<th>% Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZON/GR</td>
<td>Placebo</td>
<td>ZON/GR</td>
</tr>
<tr>
<td>Study 1: Weeks 5-12</td>
<td>-25%*</td>
<td>-19%</td>
</tr>
<tr>
<td>Study 2: Weeks 5-12</td>
<td>-22%*</td>
<td>-18%</td>
</tr>
<tr>
<td>Study 3: Weeks 5-12</td>
<td>-21%*</td>
<td>-18%</td>
</tr>
</tbody>
</table>

Table 2: Median % Reduction in All Partial Seizures and % Responders for Dose Analysis in Study 1: Intact-1 to-Treatment Analysis

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Median % Reduction in Partial Seizures</th>
<th>% Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZON/GR</td>
<td>Placebo</td>
<td>ZON/GR</td>
</tr>
<tr>
<td>1-400 mg/day</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>Weeks 1-6</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Titration</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>ZON/GR</td>
<td>Placebo</td>
<td>ZON/GR</td>
</tr>
<tr>
<td>400-600 mg/day</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>Weeks 1-6</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Titration</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 3: Risk by indication for antiepileptic drugs in the pooled analysis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events Per 1000 Patients</th>
<th>Drug Patients with Events Per 1000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events Per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.9</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials (Events that occurred in at least 2% of Zonisamide treated patients and occurred more frequently in Zonisamide treated than placebo-treated patients)

<table>
<thead>
<tr>
<th>BODY SYSTEM/PREFERRED TERM</th>
<th>Zonisamide (n=205)</th>
<th>Placebo (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BODY AS A WHOLE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Flu Syndrome</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>DIGESTIVE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>HEMATOLOGIC AND LYMPHATIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ekchymosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>METABOLIC AND NUTRITIONAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>NEUROVASCULAR AND COGNITIVE DYSFUNCTION-ALTERED COGNITIVE FUNCTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty Concentrating</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Difficulty with Memory</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Mental Slow</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (NON-PYSCHOSIS-RELATED)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation/Instability</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Depression</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (PSYCHOSIS-RELATED)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenic/Psychoses/Depression</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-CNS DEPRESSION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Tiredness</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td><strong>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-SPEECH AND LANGUAGE ABNORMALITIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speech Abnormalities</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Difficulties in Verbal Expression</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>SKIN AND APPENDAGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>SPECIAL SENSES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Taste / Smell</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1 presents the proportion of patients (Y-axis) whose percentage reduction from baseline in the all partial seizure rate was at least as great as that indicated on the Y-axis in the second and third placebo-controlled trials. 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,
No differences in efficacy based on age, sex or race, as measured by a change in seizure frequency from baseline, were detected.

INDICATIONS AND USAGE
Zonisamide capsules USP are indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

CONTRAINDICATIONS
Zonisamide capsules are contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide.

WARNINGS
Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred, although rarely, 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. Such reactions may occur when a sulfonamide is re-administered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue zonisamide immediately. Specific experience with sulfonamide-type adverse reactions to zonisamide is described below.

Serious Skin Reactions:
Consideration should be given to discontinuing zonisamide in patients who develop an otherwise unexplained rash. If the drug is not discontinued, patients should be observed frequently. 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 post-marketing 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, 6 of 205 (2.9%) zonisamide patients discontinued treatment because of rash compared to 1.5% on 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 study drug discontinuation was reported in 2.0% of patients (27.8 events per 1000 patient years). Rash usually occurred early in treatment, with 8% reported within 16 weeks in the US and European studies and 9% reported within weeks in the Japanese studies. There was no apparent relationship of dose to the occurrence of rash.

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.

Oligohidrosis and Hyperthermia in Pediatric Patients:
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 673 pediatric patients, an incidence of 1 case per 265 patient-years of exposure. While there were no cases reported in the US or European development programs, fewer than 10 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. There have been no reported deaths.

Pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with zonisamide should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather. Caution should be used when zonisamide is prescribed with drugs that impair sweating.

The practitioner should be aware that the safety and effectiveness of zonisamide in pediatric patients have not been established, and that zonisamide is not approved for use in pediatric patients.

Suicidal Behavior and Ideation
Antiepileptic drugs (AEDs), including zonisamide, 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.

Suicidal behavior and ideation have been 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 AEDs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action 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 to 100 years) in the clinical trials analyzed.

Table 3 shows absolute and relative risk by indication for all evaluated AEDs.
PRECAUTIONS

should be taken by patients if they drive, operate machinery, or perform any hazardous task.

Some manifestations of acute or chronic metabolic acidosis include hyperpnea, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or syncope. Chronic, unrelieved, metabolic acidosis may increase the risk for nephrocalcinosis or nephrolithiasis. Nephrocalcinosis 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 PRECAUTIONS, Laboratory Tests subsection).

Seizures on Withdrawal:

As with other AEDs, abrupt withdrawal of zonisamide in patients with epilepsy may precipitate increased seizure frequency or status epilepticus. Dose reduction or discontinuation of zonisamide should be done gradually.

Teratogenicity:

Women of child-bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal 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 PRECAUTIONS, Pregnancy subsection).

Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see PRECAUTIONS, Pregnancy subsection). 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 to be 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, diuretics, ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of zonisamide.

Serum bicarbonate was not measured in the controlled clinical trials of adults with epilepsy. However, serum bicarbonate was studied in three clinical trials for indications in which it has been approved: a placebo-controlled trial for migraine prophylaxis in adults, a controlled trial for monotherapy in epilepsy in adults (10 to 15 years) and a placebo-controlled trial for adjunctive treatment of epilepsy in pediatric patients (3 to 15 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 200 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 persistent treatment-emergent decrease in serum bicarbonate was 2% for daily zonisamide doses of 25 mg or 100 mg, and was 4% 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 increased with higher doses. The incidence of 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 increased with higher doses. Some patients experienced moderately severe serum bicarbonate decreases 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.

Seizures on Withdrawal:

As with other AEDs, abrupt withdrawal of zonisamide in patients with epilepsy may precipitate increased seizure frequency or status epilepticus. Dose reduction or discontinuation of zonisamide should be done gradually.

Teratogenicity:

Women of child-bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal 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. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Cognitive/Neuropsychiatric Adverse Events:

Use of zonisamide is frequently associated with central nervous system-related adverse events. The most significant of these can be classified into three general categories: 1) psychiatric symptoms, including depression and psychosis, 2) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties, and 3) somnolence or fatigue. Psychomotor slowing and difficulties with concentration occurred in the first month of treatment and were associated with doses above 300 mg/d. Speech and language problems tended to occur after 6 to 10 weeks of treatment and at doses above 300 mg/d. Although in most cases these events were of mild to moderate severity, they led to withdrawal from treatment in 1% of patients enrolled in controlled trials. Somnolence and fatigue occurred within the first 6 months of treatment. Somnolence and fatigue occurred most frequently at doses of 300 to 500 mg/d. Patients should be cautioned about this possibility and special care should be taken by patients if they drive, operate machinery, or perform any hazardous task.

PRECAUTIONS
CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of zonisamide cimetidine (300 mg four times a day for 12 days). The half-life of zonisamide in patients with hepatic and renal dysfunction (see CLINICAL PHARMACOLOGY, Special Populations subsection).

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.), a rate of 4.1 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 none of the 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 24.1 per 1000 patient-years of exposure after 12 months of use. There were 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, Metabolic Acidosis subsection).

The analytes were composed of calcium and oxalate. 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 zonisamide.

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, Metabolic Acidosis subsection).

Effect on Renal Function:
In several clinical studies, zonisamide was associated with a statistically significant 3% 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 end-stage acute renal failure in clinical development in the United States, 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 to 3 weeks of drug discontinuation. There is no information about reversibility, after drug discontinuation, of the effects on GFR after long-term. Zonisamide should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in the creatinine/BUN concentration.

Zonisamide 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.

Sudden Unexplained Death in Epilepsy:
During the development of zonisamide, new sudden unexplained deaths occurred among 991 patients with epilepsy receiving zonisamide for whom accurate exposure data are available. This represents an incidence of 7.7 deaths per 1000 patient-years. Although this rate exceeds that expected in a healthy population, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with refractory epilepsy not receiving zonisamide (ranging from 0.5 per 1000 patient-years for the general population of patients with epilepsy to 2 to 5 per 1000 patient-years for patients with refractory epilepsy; higher incidences range from 9 to 15 per 1000 patient-years among surgical candidates and surgical failures). Some of the deaths could represent seizure-related deaths in which the seizure was not observed.

Status Epilepticus:
Estimates of the incidence of treatment emergent status epilepticus in zonisamide-treated patients are difficult because a standard definition was not employed. Nonetheless, in one single-blind trials, 11.5% 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.

Information for Patients:
Patients should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to taking zonisamide. Patients should be instructed to take zonisamide only as prescribed.

Patients should be advised as follows (see Medication Guide):
- Zonisamide 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 zonisamide sufficient to determine whether it affects their performance.
- To determine the potential of zonisamide to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, zonisamide should be used with caution if used in combination with alcohol or other CNS depressants.
- Patients should contact their physician immediately if a sudden rash develops or seizures worsen.
- 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.
- Patients should contact their physician immediately if a child has been taking zonisamide and is not eating or sleeping or without a fever.
- Because zonisamide can cause hematological complications, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising.

- Suicidal Thinking and Behavior: Patients, their caregivers, and families should be counseled that AEDs, including zonisamide, may increase the risk of suicidal thoughts and behavior and should be advised 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.
- Patients should contact their physician immediately if they develop fast breathing, fatigue/tiredness, loss of appetite, or irregular heartbeat or palpitations (possible manifestation of metabolic acidosis).
- As with other AEDs, patients should contact their physician if they intend to become pregnant or are pregnant during zonisamide therapy. Patients should notify their physician if they intend to breast-feed or are breast-feeding an infant.

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS, Pregnancy subsection).

Laboratory Tests:
In several clinical studies, zonisamide was associated with a mean increase in the concentration of serum creatinine and blood urea nitrogen (BUN) of approximately 4% over the baseline measurement. Consideration should be given to monitoring renal function periodically (see PRECAUTIONS, Effect on Renal Function subsection).

Zonisamide increases serum chloride and alkaline phosphatase and decreases serum bicarbonate (see WARNINGS, Metabolic Acidosis subsection), phosphorus, calcium, and albumin.

Drug Interactions:
Effects of zonisamide on the pharmacokinetics of other antiepilepsy drugs (AEDs): Zonisamide had no appreciable effect on the steady-state plasma concentration of phenytoin, carbamazepine, or valproate during clinical trials. Zonisamide did not inhibit mixed-function liver oxidases (cytochrome P450, CYP) as measured in human liver microsomal preparations, in vitro. Zonisamide is not expected to interfere with the metabolism of other drugs that are metabolized by cytochrome P450 isozymes.

Effects of other drugs on zonisamide pharmacokinetics: Drugs that induce liver enzymes increase the metabolism and clearance of zonisamide and decrease its half-life. 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 to 38 hours; the half-life of zonisamide in patients concurrently on the non-enzyme inducing AED, valproate, was 46 hours. Concurrent medication with drugs that either induce or inhibit CYPP450 would be expected to alter serum concentrations of zonisamide.

Interactions with Concomitant Zonisamide single dose pharmacokinetic parameters were not affected by concomitant (300 mg four times a day for 12 days).

Drug Interactions with CNS Depressants: Concomitant administration of zonisamide and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of zonisamide to produce CNS depression, zonisamide should be used with caution if used in combination with alcohol or other CNS depressants.
**WARNINGS**

**Pharmacology, Interactions of Zonisamide with Other Carbonic Anhydrase Inhibitors**

Concomitant use of zonisamide, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., triamterene, acetazolamide or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation.

**Hyperthermia in Pediatric Patients**

Hyperthermia including fatal cases has been reported in children treated with zonisamide. The pathophysiology of hyperthermia includes decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In general, dose selection for an elderly patient differs from that of a younger subject. Other reported clinical experience has not identified differences in efficacy or safety between the elderly and younger patients.

**Use in Nursing Mothers**

Zonisamide is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from zonisamide, 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.

**Zonisamide treatment causes metabolic acidosis in humans.** The effect of zonisamide induced metabolic acidosis has not been studied in pregnancy; however, 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. Pregnant patients should be monitored for metabolic acidosis and treated if in the non-pregnant state. 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/m² basis. In rats, this dose is 1 to 2 times the MRHD on a mg/kg basis. Zonisamide was mutagenic in an in vitro chromosomal aberration assay in Chinese hamster lung cells. Zonisamide was not mutagenic in an in vivo micronucleus test in mice, mouse lymphoma tk assay, chromosomal aberration in human lymphocytes or in vivo bone marrow cytogenetics assay.

**Use in Pediatric Patients**

Single dose pharmacokinetic parameters are similar in healthy pediatric patients (ages 1 month to 16 years) and in healthy adult volunteers. Zonisamide is rapidly absorbed and peak maternal plasma zonisamide levels (5 mcg/mL) approximately 0.1 times the highest levels measured in humans receiving the MRHD. Following administration of zonisamide (10, 30, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular malformations (ventricular septal defects, cardiomegaly, various vascular and arterial anomalies) were found at doses of 30 mg/kg/day or greater. The low effect dose for malformations produced peak maternal plasma zonisamide levels (2 mg/mL) approximately equal to the highest levels measured in patients receiving the MRHD. 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 in this study. The low dose produced maternal plasma levels (12 mg/mL) about 0.25 times the highest human levels.

**Use in Labor and Delivery**

Zonisamide is not a drug that causes CNS depression, as well as other cognitive and/or neuropsychiatric adverse events. Zonisamide should be used with caution if used in combination with alcohol or other CNS depressants. If used during pregnancy, zonisamide should be used only if the potential benefit justifies the potential risk to the fetus. A variety of external, visceral, and skeletal malformations were produced in animals by prenatal exposure to zonisamide. Cardiorespiratory defects were prominent in both rats and dogs.

**Pharmacology of Zonisamide**

In cynomolgus monkeys, administration of zonisamide (10 or 20 mg/kg/day) to pregnant animals during organogenesis resulted in embryo-fetal deaths at both doses. The possibility that these deaths were due to malformations cannot be ruled out. The lowest embryotoxic dose in monkeys was associated with peak maternal plasma zonisamide levels (5 mcg/mL) approximately 0.1 times the highest levels measured in patients at the MRHD.

**PRECAUTIONS**

**Geriatic Use**

Single dose pharmacokinetic parameters are similar in elderly and young healthy volunteers (see CLINICAL PHARMACOLOGY, Special Populations subsection). 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.

**ADVERSE REACTIONS**

The most commonly observed adverse events related to treatment with zonisamide (incidence at least 4%) in controlled clinical trials and/or in uncontrolled clinical practices, in descending order of frequency were somnolence, anorexia, dizziness, ataxia, gastrointestinal toxicity, and difficulty with memory and/or concentration.

In controlled clinical trials, 12% of patients receiving zonisamide as adjunctive therapy discontinued due to an adverse event compared to 6% receiving placebo. Approximately 21% of the LHD patients with epilepsy who received zonisamide in clinical studies discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were somnolence, fatigue and/or asthenia (6%), anorexia (5%), difficulty concentrating (2%), difficulty with memory, mental slowing, nausea/vomiting (2%), and weight loss (1%). Many of these adverse events were dose-related (see WARNINGS and PRECAUTIONS).

**Adverse Event Incidence in Controlled Clinical Trials**

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<thead>
<tr>
<th>Table 4 list of treatment-emergent adverse events</th>
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Zonisamide has a long half-life (see CLINICAL PHARMACOLOGY section). 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 zonisamide overdose.

Dosage and Administration
Zonisamide is recommended as adjunctive therapy for the treatment of partial seizures in adults. Safety and efficacy in pediatric patients below the age of 16 have not been established. Zonisamide should
administered once or twice daily, using 25 mg or 100 mg capsules. Zonisamide is given orally and can be taken with or without food. Capsules should be swallowed whole.

Adults over Age 16: The prescriber should be aware that, because of the long half-life of zonisamide, up to two weeks may be required to achieve steady state levels approaching a stable dose or following dosage adjustment. Although the regimen described below is one that has been shown to be tolerated, the prescriber may wish to prolong the duration of treatment at the lower doses in order to fully assess the effects of zonisamide at steady state, noting that many of the side effects of zonisamide are more frequent at doses of 200 mg per day and above. Although there is some evidence of a greater response at doses above 200 mg/day, the increase appears small and formal dose-response studies have not been conducted.

The initial dose of zonisamide should be 100 mg daily. After two weeks, the dose may be increased to 200 mg daily for at least two weeks. It can be increased in 200 mg/day increments, with the dose stabilized for at least two weeks to achieve steady state at each level. Evidence from controlled trials suggests that zonisamide doses of 200 to 600 mg/day are effective, but there is no suggestion of increasing response above 400 mg/day (see CLINICAL PHARMACOLOGY, Clinical Studies subsection). There is little experience with doses greater than 600 mg/day.

Patients with Renal or Hepatic Disease: Because zonisamide is metabolized in the liver and excreted by the kidneys, patients with renal or hepatic disease should be treated with caution, and might require slower titration and more frequent monitoring (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED
Zonisamide is available as 100 mg two-piece hard gelatin capsules. The capsules imprinted with codes are printed in black ink. Zonisamide is available in bottles.

60 CAPSULES in a BOTTLE
(5217-301-90)
90 CAPSULES in a BOTTLE
(5217-301-90)

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature], in a dry place and protected from light.

Repackaged by
Aidarex Pharmaceuticals, LLC
Corona, CA 92880

MEDICATION GUIDE
Zonisamide Capsules, USP
(zoe’nis’a mide)

Read this Medication Guide before you start taking zonisamide capsules and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about zonisamide capsules?
Zonisamide capsules may cause serious side effects, including:
• Serious skin rash that can cause death.
• Less sweating and increase in your body temperature (fever).
• Suicidal thoughts or actions in some people.
• Increased level of acid in your blood (metabolic acidosis).
• Problems with your concentration, attention, memory, thinking, speech, or language.
• Blood cell changes such as reduced red and white blood cell counts.

These serious side effects are described below.
1. Zonisamide capsules may cause a serious skin rash that can cause death. These serious skin reactions are more likely to happen when you begin taking zonisamide capsules within the first 4 months of treatment but may occur at later times.
2. Zonisamide capsules may cause you to sweat less and to increase your body temperature (fever). You may need to be hospitalized for this. You should watch for decreased sweating and fever, especially when it is hot and especially in children taking zonisamide capsules.
3. Like other antiepileptic drugs, zonisamide may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call your health care provider right away if you have:
• a skin rash
• high fever, recurring fever, or long lasting fever
• less sweat than normal

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
• thoughts about suicide or dying
• attempt to commit suicide
• new or worsened depression
• new or worsening anxiety
• feeling agitated or restless
• panic attacks
• trouble sleeping (insomnia)
• trouble concentrating, remembering, or learning
• mood swings
• a skin rash
• feeling agitated or restless
• acting aggressive, being angry, or violent
• acting on dangerous impulses
• an extreme increase in activity and talking (mania) • other unusual changes in behavior or mood

Call a healthcare provider right away if you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?
• Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
• Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop zonisamide without first talking to a healthcare provider.
Stopping zonisamide suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).

4. Zonisamide can increase the level of acid in your blood (metabolic acidosis). If left untreated, metabolic acidosis can cause brittle or soft bones (osteoporosis, osteomalacia, osteopenia), kidney stones and can slow the rate of growth in children. Metabolic acidosis can happen with or without symptoms.

• Sometimes people with metabolic acidosis will:
  • feel tired
  • not feel hungry (loss of appetite)
  • feel changes in heartbeat
  • have trouble thinking clearly

Your healthcare provider should do a blood test to measure the level of acid in your blood before and during your treatment with zonisamide.

5. Zonisamide may cause problems with your concentration, attention, memory, thinking, speech, or language.

6. Zonisamide can cause blood cell changes such as reduced red and white blood cell counts. Call your healthcare provider if you develop fever, sore throat, upper respiratory infections.

Zonisamide capsules can cause other serious side effects. For more information ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers you. Be sure to read the section titled "What are the possible side effects of zonisamide capsules?"
Who should not take zonisamide capsules?
Do not take zonisamide capsules if you are allergic to medicines that contain sulfites.

What should I tell my healthcare provider before taking zonisamide capsules?
Before taking zonisamide capsules, tell your healthcare provider about all your medical conditions, including if you:
- have or have had depression, mood problems or suicidal thoughts or behavior
- have kidney problems
- have liver problems
- have history of metabolic acidosis (too much acid in your blood)
- have severe, brittle bones or soft bones (osteoporosis or osteopenia)
- have a growth problem
- are on a diet high in fat called a ketogenic diet
- have diarrhea

Tell your healthcare provider if you:
- are pregnant or plan to become pregnant. Zonisamide capsules may harm your unborn baby. Women who can become pregnant should use effective birth control. Tell your healthcare provider right away if you become pregnant while taking zonisamide capsules.
- You and your healthcare provider should decide if you should take zonisamide capsules while you are pregnant.
- If you become pregnant while taking zonisamide, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-800-332-1178. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- are breastfeeding or plan to breastfeed. Zonisamide can pass into your breast milk. It is not known if zonisamide in your breast milk can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take zonisamide capsules.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins or herbal supplements. Zonisamide capsules and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist each time you get a new medicine.

How should I take zonisamide capsules?
- Take zonisamide capsules exactly as prescribed. Your healthcare prescriber may change your dose. Your healthcare provider will tell you how much zonisamide to take.
- Take zonisamide capsules with or without food.
- Swallow the capsules whole.
- If you take too much zonisamide, call your local Poison Control Center or go to the nearest emergency room right away.
- Do not stop taking zonisamide without talking to your healthcare provider. Stopping zonisamide capsules suddenly can cause serious problems, including seizures that will not stop (status epilepticus).

What should I avoid while taking zonisamide capsules?
- Do not drink alcohol or take other drugs that make you sleepy or dizzy while taking zonisamide capsules until you talk to your healthcare provider. Zonisamide capsules taken with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how zonisamide affects you. Zonisamide can slow your thinking and motor skills.

What are the possible side effects of zonisamide capsules?
Zonisamide capsules can cause serious side effects including:
- The side effects mentioned above (see "What is the most important information I should know about zonisamide capsules?")
- kidney stones: back pain, stomach pain, or blood in your urine may mean you have kidney stones. Drink plenty of fluids while you take zonisamide to lower your chance of getting kidney stones.
- problems with mood or thinking (new or worse depression; sudden changes in mood, behavior, or loss of contact with reality, sometimes associated with hearing voices or seeing things that are not really there; feeling sleepy or tired; trouble concentrating; speech and language problems). Call your healthcare provider right away if you have any of the symptoms listed above.

The most common side effects of zonisamide capsules include:
- dryness
- loss of appetite
- dizziness
- problems with concentration or memory
- trouble with walking and coordination
- agitation or irritability

Side effects can happen at any time, but are more likely to happen during the first several weeks after starting zonisamide capsules.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all of the possible side effects of zonisamide capsules. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store zonisamide capsules?
- Store zonisamide capsules at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]
- dry and away from light

Keep zonisamide capsules and all medicines out of the reach of children.

General Information about the safe and effective use of zonisamide capsules
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use zonisamide for a condition for which it was not prescribed. Do not give zonisamide capsules to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about zonisamide capsules. if you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about zonisamide capsules that is written for health professionals. For more information, call Cipla Ltd. at 1-866-604-3261.

What are the ingredients in zonisamide capsules?
Active ingredient: zonisamide USP
Inactive ingredients: microcrystalline cellulose, hydroxypropyl vegetable oil, gelatin and colorments. Components of gelatin capsules (For 100 mg: titanium dioxide, gelatin and FDA/E172 red iron oxide).
Imprint ink dye (Black SW-9008/SW-9009)

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Manufactured for:
Cipla USA Inc.,
9300 S. Dadeland Blvd., Suite 1500
Miami, FL 33156
Manufactured by:
Insmed Pharmaceuticals, Inc.
(a subsidiary of Cipla Ltd.)
Hauppauge, NY 11788
Revised: 07/2016
Barcode: 861-01-2016

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL
**ZONISAMIDE**
zonisamide capsule

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**Labeler** - Aidarex Pharmaceuticals LLC (801503249)

Revised: 6/2017