Zonisamide is a carbonic anhydrase inhibitor. The contribution of this pharmacological action to the therapeutic effects of zonisamide is unknown. However, as a carbonic anhydrase inhibitor, zonisamide may cause metabolic acidosis (see WARNINGS, Metabolic Acidosis subsection).
The seizure rate was consistently higher for the zonisamide groups compared to the placebo groups. For example, the curve for placebo was at higher seizure rates compared to the effective treatment group. 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 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, the proportion of patients achieving a reduction of 20 mg/kg/day was at least as great as that indicated on the Y-axis in the second and third studies, and there was no apparent difference between daily and twice daily dosing (in different studies). Analysis of the data (first 4 weeks) during titration demonstrated statistically significant differences favoring zonisamide for doses of 400 to 600 mg/day, and there was no apparent difference between 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 to 12.

Figure 1 presents the proportion of patients (X-axis) whose percentage reduction from baseline in the primary comparison in both trials was for any dose over Weeks 5 to 12.

Table 1.  
* p<0.05 compared to placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>ZONISGRAN</th>
<th>Placebo</th>
<th>ZONISGRAN</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>100 mg</td>
<td>200 mg</td>
<td>400 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Weeks 5-12</td>
<td>0.9%</td>
<td>2.2%</td>
<td>2.2%</td>
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<tr>
<td>Study 2</td>
<td>200 mg</td>
<td>400 mg</td>
<td>600 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Weeks 5-12</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Study 3</td>
<td>400 mg</td>
<td>600 mg</td>
<td>800 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Weeks 5-12</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Table 2.  
* p<0.05 compared to placebo

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>ZONISGRAN</th>
<th>Placebo</th>
<th>ZONISGRAN</th>
<th>Placebo</th>
</tr>
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<tr>
<td>100 mg to 1000 mg</td>
<td>3.6%</td>
<td>2.2%</td>
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<tr>
<td>200 mg to 1000 mg</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
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<tr>
<td>300 mg to 1000 mg</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

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

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

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 to 100 years) in the clinical trials analyzed. 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 behavior or ideation among 10,000 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 269 (2.2%) zonisamide patients discontinued treatment because of rash compared to none on placebo. Across all trials during the US and European development, rash that led to discontinuation of zonisamide was reported in 1.8% 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 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.

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 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 underestimate 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, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Posthoc analyses of 109 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to zonisamide had approximately twice the risk (adjusted Relative Risk 2.2, 95%CI: 1.6, 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 to 100 years) in the clinical trials analyzed.

Table 3 shows absolute and relative risk by indication for all evaluated AEDs.
Patients should be cautioned about this possibility and special care should be taken in the treatment of these patients.
should be taken by patients if they drive, operate machinery, or perform any hazardous task.

PRECAUTIONS

General:

Somnolence is commonly reported, especially at higher doses of zonisamide (see WARNINGS/CNS/Neuropsychiatric Adverse Events subsection). Zonisamide is metabolized by the liver and eliminated by the kidneys; caution should therefore be exercised when administering zonisamide to patients with hepatic and renal dysfunction (see CLINICAL PHARMACOLOGY, Special Populations subsection).

Kidney Status:

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 38 per 1000 patient-years of exposure (40 patients with 1163 years of exposure). Of these, 12 were symptomatic, and 26 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, 46.2 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, Metabolic Acidosis subsection). The urinary stones were composed of calcium or uric acid. 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 noted in 6.8% 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 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 to 3 weeks of drug discontinuation. There is no information on reversibility, after drug discontinuation, of the effects on GFR after long-term use. Zonisamide should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in serum 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 Deaths in Epilepsy:

During the development of zonisamide, nine sudden unexplained deaths occurred among 991 patients with epilepsy receiving zonisamide for whom 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 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.

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)

1. 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. Because of the potential of zonisamide to cause CNS depression, as well as other cognitive and neuropsychiatric adverse events, zonisamide should be used with caution if used in combination with alcohol or other CNS depressants.

2. Patients should contact their physician immediately if a skin rash develops or seizures worsen.

3. Patients should contact their physician immediately if they develop symptoms, such as sudden back pain, abdominal pain, and/or loss of appetite, or irregular heart beat or palpitations (possible manifestations of metabolic acidosis).

4. Patients should contact their physician immediately if they develop signs or symptoms, such as increased sweating, fatigue, tremor, or other symptoms that suggest increased fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for stones.

5. Patients should contact their physician immediately if a child has been taking zonisamide and is not urinating as usual or if without a fever.

6. Because zonisamide can cause hemolysis and leukopenia, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising.

7. Patients should contact their physician immediately if they develop respiratory failure, fatigue, malaise, or headaches. Patients should not contact their physician if they intend to become pregnant or are pregnant during zonisamide therapy. Patients should contact 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 8% 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 antiepileptic drugs (AEDs). Zonisamide had no appreciable effect on the steady state plasma concentrations of phenobarbital, phenytoin, carbamazepine, or valproate during clinical trials. Zonisamide did not inhibit mixed-function oxidase enzymes (cytochrome P450), 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 30 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 CYP3A4 would be expected to alter serum concentrations of...
Zonisamide. Interaction with cimetidine: Zonisamide single dose pharmacokinetic parameters were not affected by cimetidine (300 mg four times a day for 12 days).

Drug interactions: 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 cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, zonisamide should be used with caution if used in combination with other CNS depressants.

Other Carbonic Anhydrase Inhibitors: Concomitant use of zonisamide, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., acetazolamide, dichlorphenamide) 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 CLINICAL PHARMACOLOGY, Interactions of Zonisamide with Other Carbonic Anhydrase Inhibitors subsection).

Carcinogenesis, Mutagenesis, Impairment of Fertility:
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 vitro chromosomal aberration assays in Chinese hamster ovary (CHO) cells. Zonisamide was not mutagenic or clastogenic in in vivo tests (Ames, mouse lymphoma tk assay, chromosomal aberration in human lymphocytes) or in the in vivo oral mouse spermatogonics assay.

Rats treated with zonisamide (20, 60, or 200 mg/kg/day) before mating and during the initial gestation phase showed signs of reproductive toxicity (decreased corpora lutea, implants, 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/m² basis.

Pregnancy: Pregnancy Category C (see WARNINGS, Teratogenicity subsection):
Zonisamide may cause serious adverse fetal effects, based on clinical and nonclinical data. Zonisamide was teratogenic in multiple animal species.
Zonisamide treatment causes metabolic acidosis in humans. The effect of zonisamide on 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 as in the non-pregnant state (see WARNINGS, Metabolic Acidosis subsection.)

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.

Zonisamide was teratogenic in mice, rats, and dogs and embolized in monkeys when administered during the period of organogenesis. Fetal abnormalities or embryonic death occurred in these species at zonisamide dose and maternal plasma levels similar to or lower than therapeutic levels in humans, indicating that use of this drug in pregnancy entails a significant risk to the fetus. A variety of external, visceral, and skeletal malformations were produced in animals by prenatal exposure to zonisamide. Cardiomegaly defects were prominent in both rats and dogs.

Following administration of zonisamide (30, 60, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular-renal malformations (ventricular septal defects, cardiomegaly, various valvar 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 (25 mcg/mL) about 0.5 times the highest plasma levels measured in patients receiving the maximum recommended human dose (MRHD) of 400 mg/day. In dogs, cardiovascular malformations were found in approximately 50% of all fetuses exposed to the high dose, which was associated with maternal plasma levels (44 mcg/mL) approximately equal to the highest levels measured in humans receiving the MRHD. Incidence of skeletal malformations were also increased at the high dose, and fetal growth retardation and increased frequencies of skeletal variation were seen at all doses studied. The low dose produced maternal plasma levels (12 mcg/mL) about 0.25 times the highest human levels.

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 embryo-fetal 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.

In a mouse embryo-fetal development study, treatment of pregnant animals with zonisamide (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. The low dose in this study is approximately 1.5 times the MRHD on a mg/m² basis. In rats, increased frequencies of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, decreased skeletal ossification) were observed among offspring of dams treated with zonisamide (20, 60, or 200 mg/kg/day) throughout organogenesis at all doses. The low effect dose is approximately 0.5 times the MRHD on a mg/m² basis.

Perinatal death was increased among the offspring of rats treated with zonisamide (10, 30, or 60 mg/kg/day) from the later part of gestation up to weaning at the high dose, or approximately 1.4 times the MRHD on a mg/m² basis. The no effect level of 30 mg/kg/day is approximately 0.7 times the MRHD on a mg/m² basis.

There are no adequate and well-controlled studies in pregnant women. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

To provide information regarding the effects of in utero exposure to zonisamide, physicians are advised to recommend that pregnant patients taking zonisamide enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by the patient themselves. Information on the registry can also be found at the website http://www.asdregistry.org/.

Labor and Delivery:
The effects of zonisamide on labor and delivery in humans are unknown.

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.

Pediatric Use:
The safety and effectiveness of zonisamide in children under age 16 have not been established. Cases of nephrolithiasis and hyperpyrexia have been reported (see WARNINGS, Nephrolithiasis and Hyperthermia in Pediatric Patients subsection). Zonisamide commonly causes metabolic acidosis in pediatric patients (see WARNINGS, Metabolic Acidosis subsection). Chronic uncontrolled metabolic acidosis in pediatric patients may cause nephrolithiasis and 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.

Geriatric 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 (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 due to an adverse event compared to 6% receiving placebo. Approximately 21% of the 1,336 patients 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 1,336 patients in controlled clinical trials.
Zonisamide has a long half-life (see close observation.

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 section). Due to the low protein
Zonisamide is a prescription medicine that is used with other medicines to treat partial seizures in people who have epilepsy.

**What is zonisamide?**

Zonisamide capsules can have other serious side effects. For more information ask your healthcare provider or pharmacist.

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

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.
4. Zonisamide can cause blood cell changes such as reduced red and white blood cell counts. Call your healthcare provider right away if you have:
   - a skin rash
   - high fever, recurring fever, or long lasting fever
   - less sweat than normal
5. Zonisamide can cause a loss of appetite

Do not stop zonisamide without first talking to a healthcare provider.

Call your healthcare provider if you have:

- eating less
- feeling tired
- feeling dizzy
- trouble sleeping

**What is the most important information I should know about zonisamide capsules?**

**DOSE AND ADMINISTRATION**

Zonisamide is recommended as an 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 be 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 upon reaching 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 300 mg per day and above. Although there is some evidence of greater response at doses above 100 to 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/day for at least two weeks. It can be increased to 300 mg/day and 400 mg/day, with the dose stable for at least two weeks to achieve steady state at each level. Evidence from controlled trials suggests that zonisamide doses of 100 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**

Product 71335-0486
NDC: 71335-0486-3 30 CAPSULE in a BOTTLE
NDC: 71335-0486-4 60 CAPSULE in a BOTTLE
NDC: 71335-0486-1 100 CAPSULE in a BOTTLE
NDC: 71335-0486-2 210 CAPSULE in a BOTTLE
NDC: 71335-0486-5 120 CAPSULE in a BOTTLE

**PRECAUTIONS**

**Zonisamide Capsules, USP**

(zonisamide)

Read this Medication Guide before you start taking zonisamide capsules and each time you get a refill. 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:

1. Serious skin rash that can cause death.
2. Less sweating and increase in your body temperature (fever).
3. Suicidal thoughts or actions in some people.
4. Increased level of acid in your blood (metabolic acidosis).
5. Problems with your concentration, attention, memory, thinking, speech, or language.
6. 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. Zonisamide capsules may cause a loss of appetite

**What is zonisamide?**

Zonisamide is a prescription medicine that is used with other medicines to treat partial seizures in people who have epilepsy.

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, sores in your mouth, or unusual bruising.

Zonisamide capsules can have 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?”

**Zonisamide**

Zonisamide is a prescription medicine that is used with other medicines to treat partial seizures in people who have epilepsy.
Zonisamide 100mg Capsule

Bar Code: 861-01-2016

Revised: 07/2016

(a subsidiary of Cipla Ltd.)

InvaGen Pharmaceuticals, Inc.
Miami, FL 33156

Cipla USA Inc.,
Manufactured for:

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Imprint Ink dye (Black SW-9008/SW-9009)

Components of gelatin capsules (For 100 mg: titanium dioxide, gelatin and FDA/E172 red iron oxide).

Inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, gelatin and colorants.

Active ingredient: zonisamide USP

For more information, call Cipla Ltd. at 1-866-604-3268.

Healthcare provider for information about zonisamide capsules that is written for health professionals.

If you would like more information, talk with your healthcare provider. You can ask your pharmacist or 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 provider 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 control 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:

- Drowsiness
- Loss of appetite
- Dizziness
- Problem 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 also ask your pharmacist or healthcare provider for information about zonisamide capsules that is written for health professionals.

For more information, call Cipla Ltd. at 1-866-604-3268.

What are the ingredients in zonisamide capsules?

Active ingredient: zonisamide USP

Inactive ingredients: microcrystalline cellulose, hypromellose, vegetable gum, gelatin, magnesium stearate.

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.
9100 S. Dadeland Blvd., Suite 1500
Miami, FL 33156

Manufactured by:

Infracare Pharmaceuticals, Inc.
(Wholly owned subsidiary of Cipla Ltd.)

Hauppauge, NY 11788

Revised: 07/2016

Barcode: 861-01-2016

Zonisamide 100mg Capsule
### Zonisamide

**zonisamide capsule**

**Product Information**

**Product Type**
- **HUMAN PRESCRIPTION DRUG**

**Item Code** (Source)
- **NDC:71335-0486**
- **NDC:69097-861**

**Route of Administration**
- **ORAL**

**Active Ingredient/Active Moiety**

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<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
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<tr>
<td>ZONISAMIDE</td>
<td>(UNII: 459384H98V)</td>
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**Inactive Ingredients**

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<td>GELATIN, UNSPECIFIED</td>
<td>(UNII: 2G86QN327L)</td>
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<td>TITANIUM DIOXIDE</td>
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<tr>
<td>FERRIC OXIDE RED</td>
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**Product Characteristics**

- **Color**: BROWN (brown opaque cap and white opaque body)
- **Score**: no score
- **Shape**: CAPSULE
- **Size**: 18mm
- **Flavor**: Imprint Code IG;228

**Packaging**

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<th>Marketing End Date</th>
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**Marketing Information**

**Marketing Category**: ANDA

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**Labeler**

- **Bryant Ranch Prepack (171714327)**

**Establishment**

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<td>RELABEL(71335-0486)</td>
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**Revised**: 12/2017

**Bryant Ranch Prepack**