**DESCRIPTION**

Zonisamide USP is an anticonvulsant drug chemically classified as a sulfonamide and unrelated to other anticonvulsant agents. The active ingredient is zonisamide USP, 1,2-bis(hydroxymethyl)-3-hydroxy-3-sulfonylpropene.

The empirical formula is C_{14}H_{14}N_{2}O_{6}S with a molecular weight of 271.22. Zonisamide USP is a white powder, pKa of 10.2, and is moderately soluble in water (0.00 mg/mL) and 0.1 N HCl (0.50 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, hydroxypropyl cellulose, gelatin, and colloidal. Components of gelatin capsules (For 100 mg: titanium dioxide, gelatin and FDA 72 red iron oxide). Impregn ink (Black SW 9001/SW 9005).

**CLINICAL PHARMACOLOGY**

**Mechanism of Action:**
The precise mechanism(s) by which zonisamide exerts its anticonvulsant effect is unknown. Zonisamide demonstrated anticonvulsant activity in several experimental models. In animals, zonisamide was effective against tonic extension seizures induced by maximal electroshock but ineffective against clinical seizures induced by subcutaneous pentetrazol. Zonisamide raised the threshold for generalized seizures induced by pentylenetetrazol and reduced the duration of convulsive 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 tютасic acid gel in cats or by cortical freezing in human volunteers. The relevance of these models to human epilepsy is unknown.

Zonisamide may produce these effects through action at sodium and calcium channels. In vitro pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca^2+ currents), consequently stabilizing neuronal membranes and suppressing neuronal hyperexcitability. In vivo binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor/somatostatin complex in rat forebrain and which does not produce changes in chloride flux. Other in vitro studies have demonstrated that zonisamide (10 to 30 mcg/mL) suppresses sympathetically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured spinal cord neurones) or spinal or facial spike of (3H)-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate 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 therapeutic 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 to 26 mcg/mL) are usually seen 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 1000 mg, but the Cmax 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 (V/F) of zonisamide is about 1.4 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 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 3% in the feces by day 3. Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (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 isoenzyme 3A4 (CYP3A4). Zonisamide does not induce its own metabolism. Plasma clearance of zonisamide is approximately 0.30 to 0.35 mL/min/kg in patients not receiving enzyme-inducing antiepilepsy drugs (AEDs). The clearance of zonisamide is increased to 0.5 mL/min/kg in patients concurrently on enzyme-inducing AEDs.

Renal clearance is about 0.5 mL/min. The clearance of 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 30 to 52 mL/min. Group 2 and Group 3 had creatinine clearances ranging from 14.5 to 55 mL/min and 10 to 20 mL/min, respectively. Zonisamide renal clearance decreased with decreasing renal function (1.42, 2.50, 2.23 mL/min, respectively). Marked renal impairment (creatinine clearance < 20 mL/min) was associated with an increase in zonisamide AUC of 35% (see DOSAGE AND ADMINISTRATION section).

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

**Interactions of Zonisamide with Other Antiepilepsy Drugs (AEDs):**

Concurrent medication of drugs that either induce or inhibit CYP3A4 may alter serum concentrations of zonisamide. Concomitant administration of phenytoin and carbamazepine increases zonisamide plasma clearance from 0.30 to 0.35 mL/min/kg to 0.63 to 0.65 mL/min/kg. 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 administration (see PRECAUTIONS, Drug Interactions subsection).

**Interactions of Zonisamide with Other Carbonic Anhydrase Inhibitors:**

Concomitant use of zonisamide a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., topiramate, acetazolamide or dichlorphenamide), may increase the severity of metabolic acidosis (see WARNINGS, Metabolic Acidosis subsection).

**PRECAUTIONS**

**Drug Interactions:**

Concurrent 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 0.30 to 0.35 mL/min/kg to 0.63 to 0.65 mL/min/kg. 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 administration (see PRECAUTIONS, Drug Interactions subsection).
The rate was consistently higher for the zonisamide groups compared to the placebo groups. For example, 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, 0.5 mg/day to 400 mg/day.

In the second (n = 152) and third (n = 138) studies, patients had a 2 to 3 month baseline, then were randomly assigned to placebo or zonisamide for three months. Zonisamide was introduced by administering 100 mg/day for the first week, 200 mg/day the second week, then 400 mg/day for two weeks, after which the dose (zonisamide or placebo) could be adjusted as necessary to a maximum dose of 200 mg/day or a maximum plasma level of 40 mcg/mL. In the second study, the total daily dose was given as a single daily dose. The average final maintenance doses received in the studies were 530 and 430 mg/day in the second and third studies, respectively. Both studies demonstrated statistically significant differences favoring zonisamide for doses of 400 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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Medium % Reduction in All Partial Seizures</th>
<th>% Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZONIGRAM Placebo ZONIGRAM Placebo</td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>n=98</td>
<td>n=98</td>
</tr>
<tr>
<td>Weeks 1-12</td>
<td>29.5%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Study 2</td>
<td>n=69</td>
<td>n=69</td>
</tr>
<tr>
<td>Weeks 5-12</td>
<td>29.0%</td>
<td>-3.3%</td>
</tr>
<tr>
<td>Study 3</td>
<td>n=67</td>
<td>n=67</td>
</tr>
<tr>
<td>Weeks 5-12</td>
<td>27.2%</td>
<td>-1.1%</td>
</tr>
</tbody>
</table>

* p<0.05 compared to placebo

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 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 Risk by indication for antiepileptic drugs in the pooled analysis**

**Table 2 Medium % Reduction in All Partial Seizures and % Responders for Dose Analyses in Study 1: Intent-To-Treat Analysis**

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Medium % Reduction in All Partial Seizures</th>
<th>% Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 to 600 mg/day</td>
<td>ZONIGRAM Placebo</td>
<td>ZONIGRAM Placebo</td>
</tr>
<tr>
<td>Weeks 1 to 12</td>
<td>32.8%</td>
<td>5.6%</td>
</tr>
<tr>
<td>300 mg/day</td>
<td>24.7%</td>
<td>0.2%</td>
</tr>
<tr>
<td>200 mg/day</td>
<td>20.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>100 mg/day</td>
<td>21.0%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

* p<0.05 compared to placebo

Figure 1 presents the proportion of patients (X-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, 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 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 or 100 years) in the clinical trials analyzed.

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 closely for evidence of decreased suicidal ideation or behavior, especially in patients who are at risk for suicidal ideation or behavior or who have a history of a suicidal attempt or behavior. Patients should be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any other psychological symptom that is new or has not been previously well-controlled. When monitoring for serious AEs, especially suicidal thoughts or behavior, the clinician should be alert to the need for intervention and should arrange for further evaluation, if indicated.

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 other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, anticholinergic antihistamines and drugs with antihypertensive activity.

Serious Skin Reactions

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

WARNINGS

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

SIDE EFFECTS

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

CONTRAINDICATIONS

Patients with a history of aplastic anemia and two confirmed cases of agranulocytosis in the US, European, or Japanese development programs.

Oligohidrosis and Hyperthermia in Pediatric Patients:

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

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.

Serious Hematologic Events:

Serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and epidermal necrolysis, have been reported in patients treated with zonisamide. Patients treated with any AED for any indication 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 other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, anticholinergic antihistamines and drugs with antihypertensive activity.

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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.

WARNINGS

Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred, although rarely, as a result of severe reactions in sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, (fibrinoid hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias). Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If any of hypersensitivity or other serious reactions occur, discontinue zonisamide immediately. Specific experience with sulfonamide-type adverse reaction 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 during 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 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 (12.3 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 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 463 pediatric patients, an incidence of 1 case per 285 patient-years of exposure. While there were no cases reported in the US or European development programs, fewer than 100 pediatric patients participated in these trials.

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

Decreased sweating and an elevation in body temperature above normal characterized these cases. Many cases were reported after exposure to elevated environmental temperatures, heat stroke, requiring hospitalization, was diagnosed in some cases. 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 other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, anticholinergic antihistamines and drugs with antihypertensive activity.

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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.

Posed analyses of 109 placebo-controlled clinical trials (monotherapy or adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 2.0, 95% CI 1.2-2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients and one suicide in placebo treated patients in the trials and one suicide 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 mechanism 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.
doses of 300 to 500 mg/day. Withdrawal from treatment in 0.2% of the patients enrolled in controlled trials. Somnolence and fatigue were frequently reported CNS adverse events during clinical trials with zonisamide. Although in most cases these events were of mild to moderate severity, they led to discontinuation of reported psychosis or related symptoms. Among all epilepsy patients treated with zonisamide, 0.9% were discontinued and 1.4% were hospitalized because of psychosis or psychosis-related symptoms compared to none of the placebo patients. Among all patients, whether treated with zonisamide or placebo, 2.2% of patients discontinued zonisamide or were hospitalized due to psychosis or psychosis-related symptoms.

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 embolized in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects, and embryofetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of zonisamide during pregnancy in humans may present a significant risk to the fetus (see PRECAUTIONS, Pregnancy subsection).

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 was 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.

In placebo-controlled trials, 2.2% of patients discontinued zonisamide or were hospitalized for depression compared to 0.6% of placebo patients. Among all epilepsy patients treated with zonisamide, 1.4% were discontinued and 1.0% were hospitalized because of reported depression or suicide attempts. In placebo-controlled trials, 2.2% of patients discontinued zonisamide or were hospitalized due to psychosis or psychosis-related symptoms compared to none of the placebo patients. Among all epilepsy patients treated with zonisamide, 0.9% were discontinued and 1.4% were hospitalized because of reported psychosis or related symptoms. Psychomotor slowing and difficulty with concentration occurred in the first month of treatment and were associated with doses above 300 mg/day. Speech and language problems tended to occur after 6 to 10 weeks of treatment and at doses above 300 mg/day. Although in most cases these events were of mild to moderate severity, they led to withdrawal from treatment in 0.2% of the patients enrolled in controlled trials. Somnolence and fatigue tended to occur within the first month of treatment. Somnolence and fatigue occurred most frequently at doses of 300 to 500 mg/day. Patients should be cautioned about this possibility and special care should be taken in situations requiring the highest degree of alertness.
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: Sedation 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 34 per 1000 patient-years of exposure (40 patients with 1168 years of exposure). Of these, 12 were symptomatic, and 28 were described as possible kidney stones based on sonographic detection. In nine patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonographic finding. The rate of occurrence of kidney stones was 2.8 per 1000 patient-years of exposure in the first six months, 6.2 per 1000 patient-years of exposure between 6 and 12 months, and 24.5 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 analyzed stones were composed of calcium or struvite salts. In general, increasing fluid intake and urine output can help reduce the risk of stone formation, particularly in those with predisposing risk factors. It is unknown, however, whether these measures will reduce the risk of stone formation in patient treated with zonisamide.

Although not approved in pediatric patients, sonographic findings consistent with nephrolithiasis were also observed in 6.6% 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).

Drug Interactions:

Zonisamide increases serum chloride and alkaline phosphatase and decreases serum bicarbonate (see WARNINGS, Metabolic Acidosis subsection). Zonisamide had no appreciable effect on the steady state plasma concentrations of phenytoin, carbamazepine, or valproate (see PRECAUTIONS, Drug Interactions subsection). Dose reduction of phenytoin, carbamazepine, or valproate is not required as a result of zonisamide treatment.

Acidosis

Although not approved in pediatric patients, sonographic findings consistent with nephrolithiasis were also observed in 6.6% 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).

Laboratory Tests:

In several clinical studies, zonisamide was associated with a statistically significant 8% mean increase from baseline of serum creatinine and blood urea nitrogen (BUN) compared to essentially no change in the placebo patients. The increase appeared to persist over time but was not progressive; this has been interpreted as an effect on glomerular filtration rate (GFR). There were no episodes of unexplained acute renal failure in clinical development in the US, Europe, or Japan. The decrease in GFR appeared within the first 4 weeks of treatment. In a 30-day study, the GFR returned to baseline within 2-3 weeks of drug discontinuation. There is no information about reversibility, after drug discontinuation, of the effect on GFR after long-term use. 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.

Special Populations

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 34 per 1000 patient-years of exposure (40 patients with 1168 years of exposure). Of these, 12 were symptomatic, and 28 were described as possible kidney stones based on sonographic detection. In nine patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonographic finding. The rate of occurrence of kidney stones was 2.8 per 1000 patient-years of exposure in the first six months, 6.2 per 1000 patient-years of exposure between 6 and 12 months, and 24.5 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 analyzed stones were composed of calcium or struvite salts. In general, increasing fluid intake and urine output can help reduce the risk of stone formation, particularly in those with predisposing risk factors. It is unknown, however, whether these measures will reduce the risk of stone formation in patient treated with zonisamide.

Although not approved in pediatric patients, sonographic findings consistent with nephrolithiasis were also observed in 6.6% 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 2-3 weeks of drug discontinuation. There is no information about reversibility, after drug discontinuation, of the effect on GFR after long-term use. 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 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/or 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 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.

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

5. Because zonisamide can cause hematologic complications, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising.

6. Suicide 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 depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behavior of concern should be reported immediately to healthcare providers.

7. Patients should contact their physician immediately if they develop hair thinning, fatigue/tiredness, loss of appetite, or irregular heart beat or palpitations (possible manifestations of metallic taste).

8. 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 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). Zonisamide had no appreciable effect on the steady state plasma concentrations of phenytoin, carbamazepine, or valproate during clinical trials. Zonisamide did not inhibit mixed-function liver oxidases (e.g., 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 isoenzymes.

Effect 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 36 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...
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, asthenia, agitation/reassurance, 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

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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...
Zonisamide has a long half-life (see CLINICAL PHARMACOLOGY section). Due to the low protein
Zonisamide capsules can have other serious side effects. For more information ask your healthcare provider if you develop fever, sore throat, sores in your mouth, or unusual bruising.

6. Zonisamide can cause blood cell changes such as reduced red and white blood cell counts. Call your healthcare provider between visits as needed, especially if you are worried about symptoms. Your healthcare provider should do a blood test to measure the level of acid in your blood before and during your treatment with zonisamide.

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

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

3. Like other antiepileptic drugs, zonisamide may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

2. Zonisamide capsules may cause you to sweat less and to increase your body temperature (fever). You are more likely to happen when you begin taking zonisamide capsules within the first 4 months of treatment but may occur at later times.

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.

These serious side effects are described below.

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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 healthcare provider right away if you have:

- a skin rash
- high fever, recurring fever, or long lasting fever
- loss of appetite
- have trouble thinking clearly
- not feel hungry (loss of appetite)
- feel changes in heart rate
- have trouble falling asleep
- have trouble sleeping
- have trouble sleeping (insomnia)
- new or worse irritability
- 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
- had suicidal thoughts or actions before or during treatment, but not helpful to inform your healthcare provider about your medical condition or treatment.

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 in 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 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)
- 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 capsules can have other serious side effects. For more information ask your healthcare provider if you develop fever, sore throat, sores in your mouth, or unusual bruising.
What is zonisamide?
Zonisamide is a prescription medicine that is used with other medicines to treat partial seizures in adults. It is not known if zonisamide is safe or effective in children under 16 years of age.

Who should not take zonisamide capsules?
Do not take zonisamide capsules if you are allergic to medicines that contain sulfa.

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.
- are breastfeeding. 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.
- are allergic to sulfa medicines.
- have kidney problems.
- have liver problems.
- have problems with urination.
- have a history of metabolic acidosis (too much acid in your blood).

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 problems with urination.
- have a history of metabolic acidosis (too much acid in your blood).
- have weak, brittle bones or soft bones (osteomalacia, osteopenia or osteoporosis).
- 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.
- are breastfeeding. 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.
- have kidney problems.
- have liver problems.
- have problems with urination.
- have a history of metabolic acidosis (too much acid in your blood).

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.
- 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 take zonisamide capsules 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 health care provider. Zonisamide capsules taken with alcohol or other 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.
- 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:
- dizziness.
- loss of appetite.
- drowsiness.
- problems with concentration or memory.
- problems 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 all real 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.

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.

What are the ingredients in zonisamide capsules?
Active ingredient: zonisamide USP
Inactive ingredients: microcrystalline cellulose, hypromellose, gelatin and colorants. Compounds of gelatin capsules (For 100 mg: titanium dioxide, gelatin and FDA/E172 red iron oxide). Imprint ink dye (Blue A SW-5008SW/9003). This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Cipla USA Inc.,
1600 S. Dadeland Blvd., Suite 1500
Miami, FL 33156

Manufactured by:
ImraGen Pharmaceuticals, Inc.
(a subsidiary of Cipla Ltd.)
Hauppauge, NY 11788
Revised: 07/2016
Zonisamide capsules, USP

Active Ingredient/Active Moiety

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Inactive Ingredients

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Labeler - Cipla USA Inc. (078719707)

Registrant - Cipla USA Inc. (078719707)

Establishment

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Revised: 12/2018

Cipla USA Inc.