SAFETY DATA SHEET
ZONISAMIDE CAPSULES USP

Strength: 25, 50 & 100 mg

Pack Size: 500's, 100's and 1000's Capsules per bottle,

Revision No.: 00

EMERGENCY OVERVIEW

Each Zonisamide capsules USP 25, 50 & 100 mg intended for oral administration contains Zonisamide USP and excipients generally considered to be non-toxic and non-hazardous in small amounts under conditions of normal occupational exposure.

Section 1. IDENTIFICATION OF THE PRODUCT

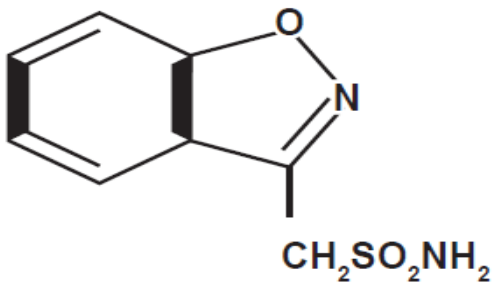
Product Name: Zonisamide capsules USP 25, 50 & 100 mg

Active Pharmaceutical Ingredient: Zonisamide USP

Formula: $C_8H_8N_2O_3S$

Chemical Name: 1,2-benzisoxazole-3-methanesulfonamide

Structure:



Manufacturer / supplier identification

Company: Cadila Healthcare Ltd. Ahmedabad, India

Address: Sarkhej – Bavla. N.H. 8A, Moraiya. Tal. Sanand. Dist. Ahmedabad – 382210.
State: Gujarat. India

Contact for information: Tel.: +91 79 6868100 Fax: +91 79 3750319

Emergency Telephone No. Tel.: +91 79 6868100

Therapeutic Category: Anti Seizure agent

Mechanism of Action: The precise mechanism(s) by which zonisamide exerts its antiseizure 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 clonic seizures induced by subcutaneous pentylenetetrazol. Zonisamide raised the threshold for generalized seizures in the kindled rat model and reduced the duration of cortical focal seizures induced by electrical stimulation of the visual cortex in cats. Furthermore, zonisamide suppressed both interictal spikes and the secondarily generalized seizures produced by cortical application of tungstic acid gel in rats or by cortical freezing in cats. 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 Ca2+ currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. *In vitro* binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion which does not produce changes in chloride flux. Other *in vitro* studies have demonstrated that zonisamide (10-30 μg/mL) suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons) or neuronal or glial uptake of [3H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. *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

Indications:

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

Recommended usage:

Pediatric Use

The safety and effectiveness of zonisamide in children under age 16 have not been established. Acute myopia and secondary angle closure glaucoma have been reported in pediatric patients. Cases of oligohidrosis and hyperpyrexia have been reported. Zonisamide commonly causes metabolic acidosis in pediatric patients. Hyperammonemia with encephalopathy has been reported in pediatric patients. Chronic untreated metabolic acidosis in pediatric patients may cause nephrolithiasis and/or nephrocalcinosis, osteoporosis and/or osteomalacia (potentially resulting in rickets), and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of zonisamide on growth and bone-related sequelae has not been systematically investigated.

Geriatric Use

Single dose pharmacokinetic parameters are similar in elderly and young healthy volunteers. 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.

Restriction on Use / Contraindications: Zonisamide capsules are contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide

Section 2. HAZARDS IDENTIFICATION

DOSAGE AND ADMINISTRATION: Zonisamide capsules are recommended as adjunctive therapy for the treatment of partial seizures in adults. Safety and efficacy in pediatric patients below the age of 16 have not been established. Zonisamide capsules should be administered once or twice daily, using 25 mg, 50 mg or 100 mg capsules. Zonisamide capsules are 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 100-200 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 100-600 mg/day are effective, but there is no suggestion of increasing response above 400 mg/day. 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

ADVERSE EFFECTS: The most commonly adverse reactions 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 reaction compared to 6% receiving placebo. Approximately 21% of the 1,336 patients with epilepsy who received zonisamide in clinical studies discontinued treatment because of an adverse reaction. The most common adverse reactions leading to discontinuation were somnolence, fatigue and/or ataxia (6%), anorexia (3%), difficulty concentrating (2%), difficulty with memory, mental slowing, nausea/vomiting (2%), and weight loss (1%). Many of these adverse reactions were dose-related

Other Adverse Reactions in Clinical Trials

Zonisamide has been administered to 1,598 individuals during all clinical trials, only some of which were placebo-controlled. The frequencies represent the proportion of the 1,598 individuals exposed to zonisamide who experienced an event on at least one occasion. All events are included except**,** trivial events, those too general to be informative, and those not reasonably associated with zonisamide.

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

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

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

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

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

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

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

Nervous System:

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

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

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

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

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

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

POST MARKETING EXPERIENCE

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

Acute pancreatitis, rhabdomyolysis, increased creatine phosphokinase, drug reaction with eosinophilia and systemic symptoms (DRESS), acute myopia and secondary angle closure glaucoma, and hyperammonemia and encephalopathy

OVER DOSE EFFECT:

Human Experience

Experience with zonisamide daily doses over 800 mg/day is limited. During zonisamide clinical development, three patients ingested unknown amounts of zonisamide as suicide attempts, and all three were hospitalized with CNS symptoms. One patient became comatose and developed bradycardia, hypotension, and respiratory depression; the zonisamide plasma level was 100.1 mcg/mL measured 31 hours post-ingestion. Zonisamide plasma levels fell with a half-life of 57 hours, and the patient became alert five days later.

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. Due to the low protein binding of zonisamide (40%), renal dialysis may be effective. The effectiveness of renal dialysis as a treatment of overdose has not been formally studied. A poison control center should be contacted for information on the management of zonisamide overdosage.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of zonisamide has not been evaluated in human studies. In a series of animal studies, zonisamide did not demonstrate abuse liability and dependence potential. Monkeys did not self-administer zonisamide in a standard reinforcing paradigm. Rats exposed to zonisamide did not exhibit signs of physical dependence of the CNS-depressant type. Rats did not generalize the effects of diazepam to zonisamide in a standard discrimination paradigm after training, suggesting that zonisamide does not have abuse potential of the benzodiazepine-CNS depressant type.

PREGNANCY COMMENTS:

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 induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) may be associated with decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus's ability to tolerate labor. Pregnant patients should be monitored for metabolic acidosis and treated as in the non-pregnant state.

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 embryolethal in monkeys when administered during the period of organogenesis. Fetal abnormalities or embryo-fetal deaths occurred in these species at zonisamide dosage 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 was produced in animals by prenatal exposure to zonisamide. Cardiovascular defects were prominent in both rats and dogs.

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 capsules, physicians are advised to recommend that pregnant patients taking zonisamide capsules 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 patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Labor and Delivery

The effect of zonisamide on labor and delivery in humans is not known.

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 drug, taking into account the importance of the drug to the mother.

Teratogenicity

Women of child bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of zonisamide during pregnancy in humans may present a significant risk to the fetus. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

WARNINGS & PRECAUTIONS:

Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred, although rarely, as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If signs 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.

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 U.S., European, or Japanese development programs. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multi-organ hypersensitivity, has occurred with zonisamide. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Zonisamide should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Oligohidrosis and Hyperthermia in Pediatric Patients

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

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, carbonic anhydrase inhibitors and drugs with anticholinergic activity.

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.

Acute Myopia and Secondary Angle Closure Glaucoma

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

Symptoms in reported cases have included acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with ciliochoroidal effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within one month after initiating zonisamide therapy.

In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with zonisamide has been reported both in pediatric patients and in adults. The primary treatment to reverse symptoms is discontinuation of zonisamide as rapidly as possible, according to the judgment of the treating physician. Other therapeutic measures, in conjunction with discontinuation of zonisamide, may be helpful. Myopia and secondary angle closure glaucoma usually resolve or improve after discontinuation of zonisamide.

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.

Metabolic Acidosis

Zonisamide causes hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis). This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase.

Generally, zonisamide-induced metabolic acidosis occurs early in treatment, but it can develop at any time during treatment. Metabolic acidosis generally appears to be dose-dependent and can occur at doses as low as 25 mg daily.

Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of zonisamide.

Some manifestations of acute or chronic metabolic acidosis include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or

more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated, metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis. Nephrolithiasis has been observed in the clinical development program in 4 % of adults treated with zonisamide, has also been detected by renal ultrasound in 8 % of pediatric treated patients who had at least one ultrasound prospectively collected, and was reported as an adverse event in 3 % (4/133) of pediatric patients. Metabolic acidosis can also increase the risk for hyperammonemia, particularly in the presence of drugs which can cause hyperammonemia.

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

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

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

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.

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.

Hyperammonemia and Encephalopathy

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

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

Measure serum ammonia concentration if signs or symptoms (e.g., unexplained change in mental status, vomiting, or lethargy) of encephalopathy occur. Hyperammonemia resulting from zonisamide resolves when zonisamide is discontinued. Hyperammonemia from zonisamide may resolve or decrease in severity with a decrease of the daily dose.

PRECAUTIONS

General

Somnolence is commonly reported, especially at higher doses of zonisamide. 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.

Kidney Stones

Information for Patients

Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking zonisamide capsules. Instruct patients to take zonisamide capsules only as prescribed.

Advise patients as follows:

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 physicians immediately if a skin rash develops.
3. Instruct patients to seek immediate medical attention if they experience blurred vision, visual disturbances, or periorbital pain.
4. 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.

5. Patients should contact their physician immediately if a child has been taking zonisamide and is not sweating as usual with or without a fever.
6. Because zonisamide can cause hematological complications, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising.
7. Counsel patients and caregivers that AEDs, including zonisamide, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.
8. Warn patients about the possible development of hyperammonemia with or without encephalopathy. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy and/or vomiting. Instruct patients to contact their physician if they develop unexplained lethargy, vomiting, or changes in mental status
9. Patients should contact their physician immediately if they develop fast breathing, fatigue/tiredness, loss of appetite, or irregular heart beat or palpitations, which are possible manifestations of metabolic acidosis.
10. 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 .
11. Encourage patients 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

Drug Interactions:

Drug Interactions with CNS Depressants: Concomitant administration of zonisamide and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of zonisamide to 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.

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 and may also increase the risk of kidney stone formation or the risk of hyperammonemia. Therefore, if zonisamide is given concomitantly with another carbonic anhydrase inhibitor, the patient should

be monitored for the appearance or worsening of metabolic acidosis

Section 3. COMPOSITION / INFORMATION ON INGREDIENTS

Component	Exposure	CAS No.
Principle Component :		
Zonisamide	Not Found	68291-97-4
Inactive ingredients :		
Microcrystalline cellulose	Not Found	9004-34-6
Sodium Lauryl sulphate	Not Found	151-21-3
Purified water	Not Found	7732-18-5
Hydrogenated vegetable oil	Not Found	68334-28-1
FD&C Blue#1	Not Found	3844-45-9
FD&C Red#4	Not Found	4548-53-2
Gelatin	Not Found	9000-70-8
Titanium dioxide	Not Found	13463-67-7
Capsule ingredients :		
Black Iron oxide	Not Found	1317-61-9
Potassium Hydroxide	Not Found	1310-58-3
Propylene Glycol	Not Found	57-55-6
Shellac	Not Found	9000-59-3.

Section 4. FIRST - AID MEASURES

Description of First Aid Measures

Eye Contact: Flush with water while holding eyelids open for at least 15 minutes. Seek medical attention immediately.

Skin Contact: Remove contaminated clothing. Flush area with large amounts of water. Use soap. Seek medical attention.

Ingestion: Never give anything by mouth to an unconscious person. Wash out mouth with water. Do not induce vomiting unless directed by medical personnel. Seek medical attention immediately.

Inhalation: Remove to fresh air and keep patient at rest. Seek medical attention immediately.

Section 5. FIRE FIGHTING MEASURES

Extinguishing Media: Use carbon dioxide, dry chemical, or water spray.

Hazardous Combustion Formation of toxic gases is possible during heating or fire.

Products:	
Fire Fighting Procedures:	During all firefighting activities, wear appropriate protective equipment, including self contained breathing apparatus.
Fire / Explosion Hazards:	Not applicable

Section 6. ACCIDENTAL RELEASE MEASURES

Health and Safety Precautions:	Personnel involved in clean-up should wear appropriate personal protective equipment. Minimize exposure.
Measures for Cleaning / Collecting:	Contain the source of spill if it is safe to do so. Collect spilled material by a method that controls dust generation. A damp cloth or a filtered vacuum should be used to clean spills of dry solids. Clean spill area thoroughly.
Measures for Environmental Protections:	Place waste in an appropriately labelled, sealed container for disposal. Care should be taken to avoid environmental release.
Additional Consideration for Large Spills:	Non-essential personnel should be evacuated from affected area. Report emergency situations immediately. Clean up operations should only be undertaken by trained personnel.

Section 7. HANDLING AND STORAGE

Storage	Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. Keep in dry place and protect from light.
Specific end use	Pharmaceutical drug product
Precautions for safe handling	If capsules are crushed and/or broken, avoid breathing dust and avoid contact with eyes, skin, and clothing. Use appropriate ventilation. Avoid generating airborne dust. When handling, use appropriate personal protective equipment. Wash thoroughly after handling. Releases to the environment should be avoided. Review and implement appropriate technical and procedural waste water and waste disposal measures to prevent occupational exposure or environmental releases. Potential points of process emissions of this material to the atmosphere should be controlled with dust collectors, HEPA filtration systems or other equivalent controls.

Section 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Engineering Controls:	Engineering controls should be used as the primary means to control exposures. General room ventilation is adequate unless the process generates dust, mist or fumes. Keep airborne contamination levels below the exposure limits listed above in this section.
Environmental Exposure Controls:	Refer to specific Member State legislation for requirements under Community environmental legislation.
Personal Protective	Refer to applicable national standards and regulations in the selection and

Equipment:	use of personal protective equipment (PPE).
Hands:	Impervious gloves are recommended if skin contact with drug product is possible and for bulk processing operations.
Eyes:	Wear safety glasses or goggles if eye contact is possible.
Skin:	Impervious protective clothing is recommended if skin contact with drug product is possible and for bulk processing operations.
Respiratory protection:	If the applicable Occupational Exposure Limit (OEL) is exceeded, wear an appropriate respirator with a protection factor sufficient to control exposures to below the OEL.

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance

Physical state Capsules

Description

Zonisamide Capsules USP, 25 mg are white to off white granular powder filled in size '4' hard gelatin capsules with pink colored cap printed with "ZA-31" in black ink and white colored body printed with "25 mg" in black ink, which are supplied as follows.

NDC 72578-040-01 in bottles of 100's capsules with child-resistant closure
NDC 72578-040-05 in bottles of 500's capsules

Zonisamide Capsules USP, 50 mg are white to off white granular powder filled in size '3' hard gelatin capsules with pink colored cap printed with "ZA-32" in black ink and white colored body printed with "50 mg" in black ink, which are supplied as follows.

NDC 72578-041-01 in bottles of 100's capsules with child-resistant closure
NDC 72578-041-05 in bottles of 500's capsules

Zonisamide Capsules USP, 100 mg are white to off white granular powder filled in size '1' hard gelatin capsules with pink colored cap printed with "ZA-33" in black ink and white colored body printed with "100 mg" in black ink, which are supplied as follows.

NDC 72578--042-01 in bottles of 100's capsules with child-resistant closure
NDC 72578-042-05 in bottles of 500's capsules
NDC 72578-042-10 in bottles of 1,000's capsules

Pure/Mixture Mixture

Section 10. STABILITY AND REACTIVITY

The product is stable

Section 11. TOXICOLOGICAL INFORMATION

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/m2 basis. Zonisamide was mutagenic in an *in vitro* chromosomal aberration assay in CHL cells. Zonisamide was not mutagenic or clastogenic in other in vitro assays (Ames, mouse lymphoma tk assay, chromosomal aberration in human lymphocytes) or in the in vivo rat bone marrow cytogenetics assay. Rats treated with zonisamide ((20 mg/kg, 60 mg/kg or 200 mg/kg) before mating and during the initial gestation phase showed signs of reproductive toxicity (decreased corpora lutea, implantations, and live fetuses) at all doses. The low dose in this study is approximately 0.5 times the maximum recommended human dose (MRHD) on a mg/m2 basis.

Section 12. ECOLOGICAL INFORMATION

Environmental Overview:	Environmental properties have not been investigated. Releases to the environment should be avoided.

Section 13. DISPOSAL CONSIDERATION

Disposal Recommendations	Dispose of waste in accordance with all applicable laws and regulations. Member State specific and Community specific provisions must be considered. Considering the relevant known environmental and human health hazards of the material, review and implement appropriate technical and procedural waste water and waste disposal measures to prevent occupational exposure and environmental release. It is recommended that waste minimization be practiced. The best available technology should be utilized to prevent environmental releases. This may include destructive techniques for waste and wastewater.

Section 14. TRANSPORT INFORMATION

The following refers to all modes of transportation unless specified below. Not regulated for transport under USDOT, EUADR, IATA, or IMDG regulations.

Section 15. REGULATORY INFORMATION

Generic Medicine, ANDA Number	77-625

Section 16. OTHER INFORMATION

Classification system:

NFPA ratings (scale 0 - 4)

Health	2
Fire	0
Reactivity	0

HMIS-ratings (scale 0 - 4)

Health	2
Fire	0
Reactivity	0

Hazard statements

H302 Harmful if swallowed.

H361 Suspected of damaging fertility or the unborn child. ·

Precautionary statements

P201 Obtain special instructions before use.

P202 Do not handle until all safety precautions have been read and understood. P264 Wash thoroughly after handling.

P270 Do not eat, drink or smoke when using this product.

P280 Wear protective gloves/protective clothing/eye protection/face protection. P301+P312 If swallowed: Call a poison center/doctor if you feel unwell.

P330 Rinse mouth.

P308+P313 IF exposed or concerned: Get medical advice/attention. P405 Store locked up.

P501 Dispose of contents/container in accordance with local/regional/national/international regulations.

Date of issue: 01st June, 2022 **Supersedes edition:** NA

The information presented in the safety data sheet is, to the best of our knowledge, accurate and reliable. It characterizes the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product.