APPROVED
Order of Ministry of
Health of Ukraine
02.09.2024 № 1524
Registration Certificate
№ UA/17907/01/01
№ UA/17907/01/02
№ UA/17907/01/03

INSTRUCTION
for medical use

ZORESAN®

Composition:
active substance: zonisamide;
1 hard capsule contains zonisamide 25 mg, or 50 mg or 100 mg;
excipients:
microcrystalline cellulose, sodium lauryl sulphate, colloidal silicon dioxide anhydrous, hydrogenated castor oil;
capsule shell:
Hard capsule 25 mg or 50 mg: gelatine, purified water, iron oxide yellow (E 172), iron oxide black (E 172), titanium dioxide (E 171), sodium lauryl sulphate;
Hard capsule 100 mg: gelatine, purified water, iron oxide red (E 172), titanium dioxide (E 171), sodium lauryl sulphate.

Pharmaceutical form. Hard capsules.
Basic physical and chemical properties:
hard capsules 25 mg: hard gelatine capsule size '4' capsule, with opaque grey cap and opaque white body, containing white to off white colour powder;
hard capsules 50 mg: hard gelatine capsule size '3' capsule, with opaque grey cap and opaque white body, containing white to off white colour powder;
hard capsules 100 mg: hard gelatine capsule size '1' capsule, with opaque red cap and opaque white body, containing white to off white colour powder.

Pharmacotherapeutic group. Antiepileptics. Other antiepileptics. Zonimsamide. ATC code N03 AX15.

Pharmacological properties.
Pharmacodynamics.
Zonisamide is an antiepileptic drug, derivative of benzisoxazole. It weakly inhibits carbonic anhydrase *in vitro* and it is chemically unrelated to other anti-epileptic agents.
Mechanism of action.
The mechanism of action of zonisamide is not fully elucidated, but it appears to act on voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on GABA-mediated neuronal inhibition.
Pharmacodynamic effects.

The anticonvulsant activity of zonisamide has been evaluated in a variety of models, in several species with induced or innate seizures, and zonisamide appears to act as a broad-spectrum anti-epileptic in these models. Zonisamide prevents maximal electroshock seizures and restricts seizure spread, including the propagation of seizures from cortex to sub-cortical structures and suppresses epileptogenic focus activity. Unlike phenytoin and carbamazepine however, zonisamide acts preferentially on seizures originating in the cortex.

Pharmacokinetic properties.

Absorption.

Zonisamide is almost completely absorbed after oral administration, reaching C_{max} peak plasma and serum concentrations within 2 to 5 hours of dosing. The first-pass metabolism is believed to be negligible. Absolute bioavailability is estimated to be approximately 100%. Oral bioavailability is not affected by food, although C_{max} peak plasma and serum concentrations may be delayed.

Zonisamide AUC and C_{max} values increased almost linearly after single dose over the dose (range of 100–800 mg) and after multiple doses (over the dose range of 100–400 mg once daily). The increase at steady state was slightly more than expected on the basis of dose, probably due to the saturable binding of zonisamide to erythrocytes. Steady state was achieved within 13 days. Slightly greater than expected accumulation occurs relative to single dosing.

Distribution.

Zonisamide is 40–50 % bound to human plasma proteins. The results of *in vitro* studies have shown that the presence of various antiepileptic drugs (for example, phenytoin, phenobarbital, carbamazepine and sodium valproate) does not affect the degree of binding of zonisamide to blood plasma proteins. The apparent volume of distribution is about 1.1–1.7 l/kg in adults indicating that zonisamide is extensively distributed to tissues. Erythrocyte/plasma ratios are about 15 at low concentrations and about 3 at higher concentrations.

Biotransformation.

Zonisamide is metabolised primarily through reductive cleavage of the benzisoxazole ring of the parent drug by CYP3A4 to form 2-sulphamoylacetylphenol (SMAP) and also by N-acetylation. Zonisamide and SMAP can additionally be glucuronidated. The metabolites, which could not be detected in plasma, are devoid of anticonvulsant activity. There is no evidence that zonisamide induces its own metabolism.

Elimination.

Apparent clearance of zonisamide at steady-state after oral administration is about 0.70 l/h and the terminal elimination half-life is about 60 hours (in the absence of CYP3A4 inducers). The elimination half-life was independent of dose and not affected by repeat administration. Fluctuation in serum or plasma concentrations over a dosing interval is low (< 30%). The main route of excretion of zonisamide metabolites and unchanged drug is via the urine. Renal clearance of unchanged zonisamide is relatively low (approximately 3.5 ml/min); about 15–30% of the administered dose is eliminated unchanged.

Linearity/non-linearity.

Zonisamide exposure increases with time until steady state is achieved by approximately 8 weeks. Subjects of higher total body weight appear to have lower steady-state serum concentrations, but this effect appears to be relatively modest. Age (≥ 12 years) and gender, after adjustment for body weight effects, have no apparent effect on zonisamide exposure in epileptic patients during steady-state dosing. There is no need for dose adjustment with any of the AEDs including CYP3A4 inducer.

Pharmacokinetic/pharmacodynamic relationship.

Zonisamide lowers the 28-day average seizure frequency and the decrease is proportional (log-linear) to zonisamide average concentration.

Special patient groups.

Renal impairment.
In subjects with renal impairment, renal clearance of single doses of zonisamide was positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance <20 ml/min.
Patients with an impaired liver function.
The pharmacokinetics of zonisamide in patients with impaired liver function have not been adequately studied.
Elderly patients.
No clinically significant differences were observed in the pharmacokinetics between young (aged 21–40 years) and elderly (65–75 years).
Children (5-18 years).
Limited data indicate that pharmacokinetics of zonisamide in children is similar to those observed in adults.

Clinical characteristics.
***Indications*.**
Zoresan® is indicated as:

- monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy;
- adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.

Contraindications.
Hypersensitivity to the active substance, to any of the excipients or to sulphonamides.

Interaction with other medicinal products and other forms of interaction.
Effect of zonisamide on cytochrome P450 enzymes
In vitro studies using human liver microsomes show no or little (<25%) inhibition of cytochrome P450 isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 at zonisamide levels approximately two-fold or greater than clinically relevant unbound serum concentrations. Therefore, zonisamide is not expected to affect the pharmacokinetics of other medicinal products via cytochrome P450-mediated mechanisms, as demonstrated for carbamazepine, phenytoin, ethinylestradiol and desipramine *in vivo*.
Potential for zonisamide to affect other medicinal products
Anti-epileptic medicinal products.
In epileptic patients, steady-state dosing with zonisamide resulted in no clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, or sodium valproate.
Oral contraceptives.
In clinical studies in healthy subjects, steady-state dosing with zonisamide did not affect serum concentrations of ethinylestradiol or norethisterone in a combined oral contraceptive.
Carbonic anhydrase inhibitors.
Zonisamide should be used with caution in adult patients treated concomitantly with carbonic anhydrase inhibitors such as topiramate and acetazolamide, as there are insufficient data to rule out a possible pharmacodynamic interaction (see section “Special warnings”). Zonisamide should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide (see section “Special warnings”).
P-gp substrate.
An *in vitro* study shows that zonisamide is a weak inhibitor of P-gp (MDR1) with an IC_{50} of 267 µmol/l and there is the theoretical potential for zonisamide to affect the pharmacokinetics of substances which are P-gp substrates. Caution is advised when starting or stopping zonisamide

treatment or changing the zonisamide dose in patients who are also receiving medicinal products which are P-gp substrates (e.g. digoxin, quinidine).

Potential medicinal product interactions affecting zonisamide.

In clinical studies, it was established that co-administration of lamotrigine with zonisamide does not have a apparent effect on the pharmacokinetics of the latter. Co-administration of zonisamide with other medicinal products that may lead to urolithiasis may enhance the risk of developing kidney stones; therefore the concomitant administration of such medicinal products should be avoided.

Zonisamide is metabolised partly by CYP3A4 (reductive cleavage), and also by N-acetyl-transferases and conjugation with glucuronic acid; therefore, substances that can induce or inhibit these enzymes may affect the pharmacokinetics of zonisamide.

- Enzyme induction. Exposure to zonisamide is lower in epileptic patients receiving CYP3A4-inducing agents such as phenytoin, carbamazepine, and phenobarbitone. These effects are unlikely to be of clinical significance when zonisamide is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti- epileptic or other medicinal products are withdrawn, dose adjusted or introduced. An adjustment of the zonisamide dose may be required. Rifampicin is a potent CYP3A4 inducer. If co-administration is necessary, the patient should be closely monitored and the dose of zonisamide and other CYP3A4 substrates adjusted as needed.
- CYP3A4 inhibition. Based upon clinical data, known specific and non-specific CYP3A4 inhibitors appear to have no clinically relevant effect on zonisamide pharmacokinetic exposure parameters. Steady-state dosing of either ketoconazole (400 mg/day) or cimetidine (1200 mg/day) had no clinically relevant effects on the single-dose pharmacokinetics of zonisamide given to healthy subjects. Therefore, modification of zonisamide dosing should not be necessary when co-administered with known CYP3A4 inhibitors.

Paediatric population.

Studies of drug interactions in children have not been performed.

Special warnings and precautions for use.

Unexplained rash.

Serious rashes occur in association with zonisamide therapy, including cases of Stevens-Johnson syndrome.

Consideration must be given to discontinuing zonisamide in patients who develop an otherwise unexplained rash. All patients who develop a rash while taking zonisamide must be closely supervised, with additional levels of caution applied to those patients receiving concomitant antiepileptic agents that may independently induce skin rashes.

Withdrawal seizures.

In accordance with current clinical practice, discontinuation of zonisamide in patients with epilepsy must be accomplished by gradual dose reduction, to reduce the possibility of seizures on withdrawal. There are insufficient data for the withdrawal of concomitant antiepileptic medicines once seizure control with zonisamide has been achieved in the add-on situation, in order to reach monotherapy with zonisamide. Therefore, withdrawal of concomitant anti-epileptic medicinal products must be undertaken with caution.

Sulphonamide reactions.

Zonisamide is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune based adverse reactions that are associated with medicinal products containing a sulphonamide group include rash, allergic reaction and major haematological disturbances, including aplastic anaemia, which very rarely can be fatal.

Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. There is inadequate information to assess the relationship, if any, between dose and duration of treatment with zonisamide and these events.

Acute myopia and secondary angle closure glaucoma.

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in adult and paediatric patients receiving zonisamide. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, and ocular hyperaemia (redness) and increased intraocular pressure. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms may occur within hours to weeks of initiating therapy. Treatment includes discontinuation of zonisamide, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. Elevated intraocular pressure of any aetiology, if left untreated, can lead to serious sequelae including permanent vision loss. Caution should be used when treating patients with history of eye disorders with zonisamide.

Suicide ideation and behaviour.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for zonisamide. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Kidney stones.

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during zonisamide treatment. In addition, patients taking other drugs associated with nephrolithiasis may also be at increased risk.

Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors.

Metabolic acidosis.

Hyperchloraemic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with zonisamide treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of zonisamide in placebo-controlled clinical trials and in the post-marketing period. Generally, zonisamide-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Decrease in the level of bicarbonates is usually insignificant (average decrease of approximately 3.5 mEq/l at daily doses of 300 mg in adults); rarely patients can experience more severe decreases. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or medicinal products) may be additive to the bicarbonate lowering effects of zonisamide.

The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in younger patients. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in patients taking zonisamide who have underlying conditions which might increase the risk of acidosis, in patients who are at an increased risk of adverse consequences of metabolic

acidosis and in patients with symptoms suggestive of metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing zonisamide (by gradual discontinuation or reduction of a therapeutic dose) as osteopenia may develop.
If the decision is made to continue patients on zonisamide in the face of persistent acidosis, alkali treatment should be considered.
Metabolic acidosis during treatment with zonisamide may lead to hyperammonemia (with or without encephalopathy). The risk of hyperammonemia may be increased in patients who simultaneously take other drugs that can cause hyperammonemia (for example, valproate), or in people who have disorders of urea metabolism or reduced activity of hepatocyte mitochondria. Patients who develop unexplained lethargy or mental status changes during treatment with zonisamide should consider the risk of hyperammonemic encephalopathy and assess blood ammonia levels.
Zonisamide should be used with caution in adult patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate or acetazolamide, as there are insufficient data to rule out a pharmacodynamic interaction.
Heat stroke.
Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients. Caution should be used in adults when zonisamide is prescribed with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity.
Pancreatitis.
In patients taking zonisamide who develop the clinical signs and symptoms of pancreatitis, it is recommended that pancreatic lipase and amylase levels are monitored. If pancreatitis is evident, in the absence of another obvious cause, it is recommended that discontinuation of zonisamide be considered and appropriate treatment initiated.
Rhabdomyolysis.
In patients taking zonisamide, in whom severe muscle pain and/or weakness develop either in the presence or absence of a fever, it is recommended that markers of muscle damage be assessed, including serum creatine phosphokinase and aldolase levels. If elevated, in the absence of another obvious cause such as trauma or grand mal seizures, it is recommended that zonisamide discontinuation be considered and appropriate treatment initiated.
Women of childbearing potential.
Women of childbearing potential must use effective contraception during treatment with zonisamide and for one month after discontinuation (see section “Use during pregnancy or lactation”). Zonisamide should not be used in women of reproductive age who are not using effective contraception unless clearly necessary and only if the potential benefit is considered to be justified by the risks to the fetus. Women of reproductive age receiving zonisamide therapy should consult a specialist. They should be fully informed about the risks and benefits of zonisamide and understand the possible effects of therapy on the fetus before it is started. Also, before starting zonisamide therapy, women of reproductive age should consider a pregnancy test. In the case of planning a pregnancy, before conception and stopping contraception, a woman should consult a doctor about reviewing zonisamide therapy, including the possibility of using other treatment regimens. If a woman receiving zonisamide therapy becomes pregnant or thinks she may be pregnant, she should seek immediate medical advice.
Physicians prescribing zonisamide therapy should ensure that patients are fully informed of the need to use appropriate effective contraception. They should also make sure that oral contraceptives or doses of their components are adequate based on an individual assessment of the patient’s clinical situation.
Body weight.

Zonisamide may cause weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or is underweight whilst on this medication. If substantial undesirable weight loss occurs, discontinuation of zonisamide should be considered. Weight loss is potentially more serious in children.

Paediatric population

The warnings and precautions mentioned above are also applicable paediatric patients.

The warnings and precautions mentioned below are relevant to paediatric patients.

Heat stroke and dehydration.

Preventing overheating and dehydration in children.

Zonisamide can cause children to sweat less and overheat and if the child is not treated this can lead to brain damage and death. Children are most at risk especially in hot weather.

When a child is taking zonisamide, the precautions have to be followed:

- the child should stay cool especially in hot weather;
- the child must avoid heavy exercise especially when the weather is hot;
- the child must drink plenty of cold water;
- the child must not take any of these medicines: carbonic anhydrase inhibitors (like topiramate and acetazolamide), and anticholinergic agents (like clomipramine, hydroxyzine, diphenhydramine, haloperidol, imipramine and oxybutynin).

IN THE EVENT OF ANY OF THE FOLLOWING SYMPTOMS IN A CHILD SHOULD IMMEDIATELY SEEK EMERGENCY MEDICAL CARE AND TAKE IMMEDIATE FIRST AID MEASURES.

Symptoms:

- the skin feels hot,
- little or no sweating,
- confusion,
- muscle cramps,
- rapid heartbeat or breathing.

Immediate first aid measures:

- take the child to a cool, shaded place;
- keep the child's skin cool with water;
- give the child cold water to drink.

Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients. Heat stroke requiring hospital treatment was diagnosed in some cases. Heat stroke requiring hospital treatment and leading to death has been reported. Most reports occurred during periods of warm weather. Physicians should discuss with patients and their carers the potential seriousness of heat stroke, situations in which it might arise, as well as action to take in the event of any signs or symptoms. Patients or their carers must be warned to take care to maintain hydration and avoid exposure to excessive temperatures and strenuous physical exercise depending on the condition of the patient. Prescribers should draw the attention of paediatric patients and their parent/ carers to the advice in the instruction for medical use on preventing heat stroke and overheating in children as provided. In the event of signs or symptoms of dehydration, oligohydrosis, or elevated body temperature, discontinuation of zonisamide should be considered. Zonisamide should not be used as co-medication in paediatric patients with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity.

Body weight.

Weight loss leading to deterioration of general condition and failure to take anti-epilepsy medication has been related to a fatal outcome. Zonisamide is not recommended for paediatric patients who are underweight or have a decreased appetite. The incidence of decreased body

weight is consistent across age groups. However, given the potential seriousness of weight loss in children, weight should be monitored in this population during the treatment.
A dietary supplement or increased food intake should be considered if the patient is failing to gain weight in accordance with growth charts. Otherwise zonisamide should be discontinued.
There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above with a body weight of less than 20 kg should be treated with caution. The long-term effect of weight loss in the paediatric population on growth and development is unknown.
Metabolic acidosis.
The risk of zonisamide induced metabolic acidosis appears to be more frequent in paediatric patients. Also, clinically metabolic acidosis in this age group is more severe. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in this population. The long-term effect of low bicarbonate levels on growth and development is unknown.
Zonisamide should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide.
Nephrolithiasis.
Kidney stones (nephrolithiasis) have occurred in paediatric patients. Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during zonisamide treatment.
Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors. Renal ultrasound should be performed at the discretion of the physician. In the event kidney stones are detected, zonisamide should be discontinued.
Hepatic dysfunction.
Increased levels of hepatobiliary parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and bilirubin have occurred in paediatric patients during the treatment with zonisamide. Nevertheless, if a hepatic event is suspected, liver function should be evaluated and discontinuation of zonisamide should be considered.
Cognition.
Cognitive impairment in patients affected by epilepsy has been associated with the underlying pathology and/ or the administration of anti-epileptic treatment. In a zonisamide placebo-controlled study conducted in paediatric and adolescent patients, the proportion of patients with impaired cognition was numerically greater in the zonisamide group compared with the placebo group.
Excipients.
The medicinal product Zoresan® contains castor hydrogenated oil, which can cause stomach upset and diarrhea.

Use during pregnancy and lactation.
Women of reproductive age.
Women of reproductive age should use effective contraception during zonisamide therapy and for 1 month after its discontinuation (see section “Special warnings”).
Zonisamide should not be used in women of reproductive age who are not using effective contraception unless clearly necessary and only if the potential benefit is considered to be justified by the risks to the fetus. Women of reproductive age receiving zonisamide therapy should consult a specialist. They should be fully informed about the risks and benefits of zonisamide and understand the possible effects of therapy on the fetus before it is started. Also, before starting

zonisamide therapy, women of reproductive age should consider a pregnancy test. In the case of planning a pregnancy, before conception and discontinuing contraception, a woman should consult a doctor about reviewing zonisamide therapy, including the possibility of using other treatment regimens.
As with all antiepileptic medicines, sudden discontinuation of zonisamide should be avoided for pregnant women as this may lead to development of an epileptic seizure that could have serious consequences for the woman and the unborn child. The risk of birth defect is increased by factor 2 to 3 in the offspring of mothers treated with an antiepileptic medicinal product. The most frequently reported are cleft lip, cardiovascular malformations and neural tube defect. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy.
Pregnancy.
There are limited data from the use of zonisamide in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.
There are data of an increase in the proportion of babies born at a low birth weight, pre-term or small for gestational age. Data from pregnancy registries showed that the use of zonisamide led to an increase of approximately 5% to 8% in the proportion of children with low body weight, by 8% to 10% in the proportion of premature births and by 7% to 12% in the proportion of infants with insufficient body weight in relation to their gestational age (compared to the data of those women who received lamotrigine monotherapy).
Zonisamide must not be used during pregnancy unless the potential benefit is considered to justify the risk to the foetus. If zonisamide is prescribed during pregnancy, patients should be fully informed of the potential harm to the foetus and use of the minimal effective dose is advised along with careful monitoring.
Breast-feeding.
Zonisamide is excreted in human milk in the concentration in breast milk similar to plasma. During breastfeeding, the drug can be used only in cases where, in the opinion of the doctor, the benefits of taking zonisamide for the mother outweigh the potential risk of discontinuation of breastfeeding for the baby. Breast-feeding should be discontinued while taking the drug. Due to the long retention time of zonisamide in the body, breast-feeding must not be resumed until one month after zonisamide therapy is completed.
Fertility.
There are no clinical data available on the effects of zonisamide on human fertility. Studies in animals have shown changes in fertility parameters.

Effects on ability to drive and use machines.
No studies on the effects on the ability to drive and use machines have been performed. However, given that some patients may experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase, patients must be advised to exercise caution during activities requiring a high degree of alertness, e.g., driving or operating machines.

Posology and method of administration.
Zoresan® is used orally regardless of food intake.
Adults.
Dosage escalation and maintenance.
Zonisamide may be taken as monotherapy or added to existing therapy. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 1. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

Table 1.

Recommended dosage escalation and maintenance regimen in adults

Treatment regimen	*Dose titration phase*			*Maintenance dose*
	Week 1–2	*Week 3–4*	*Week 5–6*	
Monotherapy Newly diagnosed adult patients	100 mg/day (once a day)	200 mg/day (once a day)	300 mg/day (once a day)	300 mg/day (once a day) If a higher dose is required: increase at two-weekly intervals in increments of 100 mg up to a maximum of 500 mg.
Adjunctive therapy – with CYP3A4-inducing agents	*Week 1* 50 mg/day (in two divided doses)	*Week 2* 100 mg /day (in two divided doses)	*Week 3–5* Increase at weekly intervals in increments of 100 mg	300 to 500 mg per day (once a day or two divided doses).
Adjunctive therapy – - without CYP3A4-inducing agents or patients with renal or hepatic impairment	*Week 1–2* 50 mg/day (in two divided doses)	*Week 3–4* 100 mg/day (in two divided doses)	*Week 5–10* Increase at two-weekly intervals in increments of up to 100 mg	300 to 500 mg per day (once a day or two divided doses). Some patients may respond to lower doses.

Withdrawal.

When zonisamide treatment is to be discontinued, it should be withdrawn gradually. Dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic medicine doses (where necessary).

Paediatric population (aged 6 years and above).

Dosage escalation and maintenance.

Zonisamide must be added to existing therapy for paediatric patients aged 6 years and above. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 2. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

Attention should be drawn to children, their parents or carers to special instructions for patients on preventing heatstroke (see section “Special warnings”).

Table 2.

Recommended dosage escalation and maintenance regimen for paediatric population aged 6 years and above.

Treatment regimen	*Phase titration dose*		*Maintenance dose*	
Adjunctive therapy - with CYP3A4-inducing agents CYP3A4	*Week 1*	*Week 2–8*	*Patients with body weight from 20 to 55 kg**	*Patients with body weight > 55 kg*
	1 mg/kg/day (once a day)	Increase at weekly intervals in increments of 1 mg/kg	6 to 8 mg/kg/day (once a day)	300–500 mg/day (once a day)
Adjunctive therapy - without CYP3A4-inducing agents	*Week 1–2*	*Weeks ≥ 3*	*Patients of weight 20 to 55 kg**	*Patients of weight > 55 kg*
	1 mg/kg/day (once a day)	Increase at two-weekly intervals in increments of 1 mg/kg	6 to 8 mg/kg/day (once a day)	300–500 mg/day (once a day)

*To ensure a therapeutic dose is maintained the weight of a child should be monitored and the dose reviewed as weight changes occur (up to a weight of 55kg). The dose regime is 6-8 mg/kg/day up to a maximum dose of 500 mg/day.

The safety and efficacy of zonisamide in children aged below 6 years or those below 20 kg have not yet been established. There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above and with a body weight less than 20 kg should be treated with caution.

It is not always possible to precisely achieve the calculated dose with Zoresan®. In these cases it is therefore recommended that the Zoresan® total dose should be rounded up or down to the nearest available dose (25 mg, 50 mg and 100 mg).

Withdrawal.

In case of need to stop treatment with zonisamide, the drug should be discontinued gradually by reducing the dose by 2 mg / kg once a week (Table 3).

Table 3.

Recommended regimen for decreasing the dose of zonisamide in children over 6 years of age

Body weight	*Dose reduction at weekly intervals:*
20–28 kg	25 to 50 mg/day *
29–41 kg	50 to 75 mg/day *
42–55 kg	100 mg/day*
> 55 kg	100 mg/day*

*All doses are once daily.

Elderly.

Caution should be exercised at initiation of treatment in elderly patients as there is limited information on the use of zonisamide in these patients. Prescribers should also take account of the safety profile of zonisamide (see section “Adverse reactions”).

Patients with renal impairment.

Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients. Slower titration of zonisamide might be required. Since

zonisamide and its metabolites are excreted renally, it should be discontinued in patients who develop acute renal failure or where a clinically significant sustained increase in serum creatinine is observed.
In subjects with renal impairment, renal clearance of single doses of zonisamide was positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance < 20 ml/min.
Patients with hepatic impairment.
Use of zonisamide in patients with hepatic impairment has not been studied. Therefore, use in patients with severe hepatic impairment is not recommended. Caution must be exercised in treating patients with mild to moderate hepatic impairment, and a slower titration of zonisamide may be required.

Children.
The drug should be used in children aged 6 years and with body weight more than 20 kg.

Overdose.
Symptoms.
Cases of accidental and intentional overdose in adults and children have been reported. In some cases, overdose was asymptomatic, especially with immediate gastric lavage and artificially induced vomiting.
In other cases, the overdose was accompanied by the following symptoms: drowsiness, nausea, gastritis, nystagmus, myoclonus, coma, bradycardia, impaired renal function, arterial hypotension and respiratory depression.
A very high concentration of zonisamide in plasma (100.1 μg/ml) was noted approximately 31 hours after an overdose of zonisamide and clonazepam. A patient with an overdose of these drugs developed coma and respiratory depression. However, after 5 days the patient regained consciousness and had no complications.
Treatment.
No specific antidotes for zonisamide overdose are available. Following a suspected recent overdose, emptying the stomach by gastric lavage or by induction of emesis may be indicated with the usual precautions to protect the airway. General supportive care is indicated, including frequent monitoring of vital signs and close observation. Since zonisamide has a long half-life, the symptoms of its overdose may be persistent. Although not formally studied for the treatment of overdose, haemodialysis reduced plasma concentrations of zonisamide in a patient with reduced renal function, and may be considered as treatment of overdose if clinically indicated.

Adverse reactions.
Safety profile summary
In the course of clinical studies, zonisamide was used by more than 1,200 patients, more than 400 of whom received the drug for at least 1 year. In addition, extensive postmarketing experience with zonisamide has been accumulated in Japan since 1989 and in the United States since 2000.
It should be noted that zonisamide is a derivative of benzisoxazole, which contains a sulfonamide group. Serious adverse reactions from the immune system associated with taking drugs containing the sulfonamide group include skin rashes, allergic reactions, and severe hematological disorders, including aplastic anemia, which in very rare cases leads to death (see the section “Special warnings”).
The most common adverse reactions in controlled trials of combination therapy were somnolence, dizziness, and anorexia. The most common adverse reactions in a randomized controlled trial of zonisamide monotherapy versus long-acting carbamazepine in the zonisamide-treated group were decreased bicarbonate, loss of appetite, and weight loss. The frequency of a significant decrease

in the level of bicarbonates in the serum (decrease to the level of less than 17 mEq/L and more than 5 mEq/L) was 3.8%. The frequency of a significant decrease in body weight by 20% or more was 0.7%.

Adverse reactions associated with the use of zonisamide obtained from clinical studies and postmarketing surveillance are listed below. The frequency is classified according to the following scheme:

Very common	≥1/10
Common	from ≥1/100 to <1/10
Uncommon	from ≥1/1000 to <1/100
Rare	from ≥1/10000 to <1/1000
Very rare	<1/10000
Unknown	Cannot be estimated from available data

Table 4.

Adverse reactions associated with zonisamide obtained during clinical studies of complex therapy and post-marketing surveillance.

System-organ class	Very common	Common	Uncommon	Very rare
Infections and infestations			Pneumonia, urogenital infections	
Blood and lymphatic system disorders		Ecchymosis		Agranulocytosis, aplastic anaemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, thrombocytopenia
Immune system disorders		Hypersensitivity reactions		Drug-induced hypersensitivity syndrome, DRESS syndrome (rash with eosinophilia and systemic symptoms)
Metabolism and nutrition disorders	Anorexia		Hypokalaemia	Metabolic acidosis, renal tubular acidosis
Psychiatric disorders	Agitation, irritability, confusional state, depression	Emotional lability, anxiety, insomnia, psychotic disorders	Anger, aggression, suicidal thoughts and suicide attempts	Hallucinations
Nervous system disorders	Ataxia, dizziness, memory impairment, drowsiness	Bradyphrenia, disturbance of attention, nystagmus, paraesthesia, speech disorders, tremor	Seizures	Amnesia, coma, Grand mal seizures, myasthenic syndrome, malignant neuroleptic syndrome, status epilepticus

Eye disorders	Diplopia			Angle closure glaucoma, eye pain, myopia, blurred vision, visual acuity reduced
Respiratory, thoracic and mediastinal disorders				Dyspnoea, aspiration pneumonia, respiratory disorder, Hypersensitivity-type Pneumonitis
Gastrointestinal disorders		Abdominal pain, constipation, diarrhoea, dyspepsia, nausea	Vomiting	Pancreatitis
Hepatobiliary disorders			Cholecystitis, cholelithiasis	Hepatocellular damage
Skin and subcutaneous tissue disorders		Rashes, pruritus, alopecia		Anhidrosis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal system and connective tissue disorders				Rhabdomyolysis
Urinary system disorders		Nephrolithiasis	Urolithiasis	Hydronephrosis, renal failure, Urine abnormality
General disorders and administration site conditions		Fatigue, influenza-like illness, pyrexia, peripheral oedema.		
Investigations	Decreased bicarbonate	Weight decreased		Blood creatine phosphokinase increased, blood creatinine increased, blood urea increased, liver function tests abnormal
Injuries, poisoning and complications caused by investigation procedures				Heat stroke

In addition, there have been isolated cases of sudden unexpected death in patients with epilepsy treated with zonisamide.

Table 5.

Adverse reactions in a randomized controlled trial of monotherapy comparing zonisamide with long-acting carbamazepine.

System-organ class	Very common	Common	Uncommon
Infections and infestations			Urogenital infections, pneumonia
Blood and lymphatic system disorders			Leukopenia, thrombocytopenia
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric disorders		Agitation, depression, insomnia, mood swings, anxiety	Confusion, acute psychosis, aggression, suicidal thoughts, hallucinations
Nervous system disorders		Ataxia, dizziness, memory impairment, drowsiness, bradyphrenia, disturbance of attention, paraesthesia	Nystagmus, speech disorders, tremor, seizures
Eye disorders		Diplopia	
Respiratory, thoracic and mediastinal disorders			Respiratory disorders
Gastrointestinal disorders		Constipation, diarrhoea, dyspepsia, nausea, vomiting	Abdominal pain
Hepatobiliary disorders			Acute cholecystitis
Skin and subcutaneous tissue disorders		Rashes	Pruritus, ecchymosis
General disorders and administration site conditions		Fatigue, fever, irritability	
Investigations	Decreased bicarbonate	Weight decreased, blood creatine phosphokinase increased, alanine aminotransferase level increased, aspartate aminotransferase level increased	Urine composition impairment

Additional information regarding special groups of patients

Elderly patients

A pooled analysis of safety data in 95 elderly patients showed a relatively higher incidence of peripheral edema and pruritus compared to younger patients.

A review of post-marketing data in patients over 65 years old shows a higher frequency than in the general population of the following phenomena: Stevens-Johnson syndrome and drug-induced hypersensitivity syndrome, sudden unexpected death in patients with epilepsy.
Pediatric patients
The safety profile of zonisamide in children who participated in placebo-controlled clinical studies (aged 6 to 17 years old) is consistent with the safety profile of the drug in adults. Of 465 patients included in the pediatric safety database (including 67 patients who continued to participate in the open-label phase of the extended controlled clinical trial), death occurred in 7 children (1.5%; 14.6/1000 patient-years): in 2 cases as a result of status epilepticus, one of which was associated with a significant decrease in body weight (by 10% within 3 months) in a patient with low body weight, with the subsequent refusal to take the drug; in 1 case as a result of brain injury/hematoma and in 4 cases death occurred in patients with previous functional neurological deficits of various genesis (2 cases of sepsis associated with pneumonia/multiple organ failure, 1 case of sudden unexpected death in patients with epilepsy and 1 case of brain injury). A total of 70.4% of patients treated with zonisamide in the controlled study or in the open-label extension phase of this study had a bicarbonate level of less than 22 mmol/L at least once during therapy. Low bicarbonate levels persisted for a long time (median 188 days).
In a pooled analysis of safety data obtained from 420 children (183 from 6 to 11 years old and 237 from 12 to 16 years old, in whom the average duration of taking the drug was approximately 12 months), it was found that there were relatively more frequent reports of pneumonia, dehydration, decreased sweating, impaired biochemical indicators of liver function, otitis media, pharyngitis, sinusitis and upper respiratory tract infections, cough, epistaxis and rhinitis, abdominal pain, vomiting, rashes and eczema, as well as fever (especially in persons under 12 years of age) compared to data on adult patients. Amnesia, increased creatinine levels, lymphadenopathy, and thrombocytopenia have been reported less frequently. The frequency of weight loss by 10% or more was 10.7% (see “Special warnings” section). In some cases of weight loss, there was a delay in the transition to the next Tanner stage and maturation of bone tissue.
Adverse reactions reporting
The reporting of adverse reactions after the registration of a medicinal product is important. This makes it possible to monitor the benefit/risk ratio when using this medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives should be notified of all cases of suspected adverse reactions and lack of efficacy of the medicinal product through the Automated Pharmacovigilance Information System at the link: https://aisf.dec.gov.ua.

Shelf life.
3 years.

Storage conditions.
Store in the original package at the temperature not more than 25°C.
Keep out of reach of children.

Package.
10 capsules in a blister; 3 or 6 blisters in a carton package.

Condition of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Manufacturer's location and address of the place of business.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Date of last revision. 02.09.2024