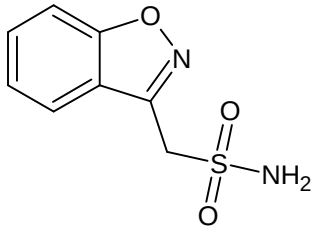
Zonegran® Product Information

Name of the medicine

Zonisamide (INN, AAN)

Zonisamide has a molecular formula $C_8H_8N_2O_3S$ and a molecular weight of 212.23. The chemical structure is:



CAS: 68291-97-4

Description

Zonisamide forms white to pale yellow crystals or a crystalline powder. It is freely soluble in acetone, sparingly soluble in methanol, slightly soluble in ethanol and very slightly soluble in water, diethyl ether and chloroform.

The inactive ingredients in Zonegran include microcrystalline cellulose, hydrogenated vegetable oil and sodium lauryl sulphate. The hard capsule shells contain gelatin, titanium dioxide (E171), shellac, propylene glycol, potassium hydroxide and black iron oxide (E172) (only in 50 mg capsules), sunset yellow FCF (E110) (only in 100 mg capsules) and allura red AC (E129) (only in 100 mg capsules).

Pharmacology

Zonisamide is a benzisoxazole derivative. It is an antiepileptic medicine with weak carbonic anhydrase inhibiting activity *in vitro*. It is chemically unrelated to other antiepileptic agents.

Pharmacodynamics

Zonisamide exhibits broad-spectrum anticonvulsant activity in a variety of animal models characterised by induced or innate seizures; it is effective against tonic (but not clonic) seizures, raises generalised seizure threshold, shortens cortical focal seizure duration, and suppresses interictal spikes and secondarily generalised seizures. Zonisamide restricts seizure spread, including propagation of seizures from the cortex to sub-cortical structures, and suppresses epileptogenic focus activity. Unlike phenytoin and carbamazepine, zonisamide acts preferentially on seizures originating in the cortex.

The mechanism of action of zonisamide has not been 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, and facilitates dopaminergic and serotonergic neurotransmission.

Pharmacokinetics

Absorption

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

Zonisamide plasma AUC and C_{max} values increased almost linearly after a 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 following a single dose and at steady state were 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 of a change in dose. Concentrations of zonisamide at steady state are up to six-fold higher than following an equivalent single dose at the recommended dosing interval.

Distribution

Zonisamide is 40 - 50 % bound to human plasma proteins, with *in vitro* studies showing that this is unaffected by the presence of various antiepileptic medicinal products (i.e., phenytoin, phenobarbitone, carbamazepine, and sodium valproate). The apparent volume of distribution is about 1.1 – 1.7 l/kg in adults indicating that zonisamide is extensively distributed to tissues. Zonisamide binds saturably to erythrocytes, and erythrocyte/plasma C_{max} ratios are about 11 at low drug concentrations in plasma and about 3 at therapeutic concentrations.

Metabolism

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 to form N-acetyl zonisamide. Parent drug 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 from plasma 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 concomitant therapy with CYP3A4 inducers. However, the apparent clearance is increased by up to 2-fold in patients also receiving the antiepileptic drugs phenobarbitone, phenytoin, carbamazepine and/or sodium valproate, and elimination half-life is reduced by up to 50%. The elimination half-life is independent of dose and not affected by repeat administration. Fluctuation in serum or plasma zonisamide concentrations over a dosing interval is low (< 30 %). The rate of clearance from erythrocytes is approximately 0.3 L/h at steady state. The main route of excretion of zonisamide metabolites and unchanged drug is via the urine. In healthy volunteers, 62% of the dose was recovered in urine and a further 3% in

faeces over 10 days. Renal clearance of unchanged zonisamide is relatively low (approximately 3.5 ml/min); about 15 - 30 % of the dose is eliminated unchanged, with the remainder being excreted as metabolites.

Effect of zonisamide on cytochrome P450 enzymes

In vitro studies using human liver microsomes show no or little (<25%) inhibition of cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4 at zonisamide concentrations approximately two-fold or greater than clinically relevant unbound serum concentrations. Clinical studies have demonstrated that zonisamide does not significantly affect the pharmacokinetics of carbamazepine, phenytoin, lamotrigine, sodium valproate, levonorgestrel, norethindrone, ethynylestradiol and desipramine *in vivo*. The potential effects of zonisamide on the pharmacokinetics of other compounds, including phenobarbitone, are unknown.

Special patient groups

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: No clinically significant differences were observed in the pharmacokinetics between young (aged 21-40 years) and elderly (65-75 years).

Adolescents (12-18 years): Limited data indicate that pharmacokinetics in adolescents dosed to steady state at 1, 7 or 12 mg/kg daily, in divided doses, are similar to those observed in adults, after adjustment for bodyweight.

Other characteristics

No clear zonisamide dose-concentration-response relationship has been defined. When comparing the same dose level, 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.

Clinical trials

Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults

Efficacy of zonisamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine prolonged release (PR) in 583 adult subjects with newly diagnosed partial seizures with or without secondary generalised tonic-clonic seizures. Subjects were randomised to carbamazepine PR (N=301; 600 to 1200 mg/day,

twice-daily) or zonisamide (N=282; 300 to 500 mg/day, once-daily), and received treatment for a duration of up to 24 months depending on response. Subjects were titrated to the initial target dose of 600 mg carbamazepine or 300 mg of zonisamide. Subjects who experienced a seizure were titrated to the next target dose i.e. 800 mg carbamazepine or 400 mg of zonisamide. Subjects who experienced a further seizure were titrated to the maximal target dose of 1200 mg carbamazepine or 500 mg zonisamide. Subjects who were seizure-free for 26 weeks at a target dose level continued on this dose for another 26 weeks.

Six-month seizure freedom was achieved in 79.4% of zonisamide-treated subjects and 83.7% of carbamazepine PR treated subjects (in the per protocol population). The adjusted absolute difference between treatments was -4.5% (95% CI: -12.2%, 3.1%). More than half of the subjects remained seizure-free at 12 months (67.6%% zonisamide versus 74.7%).

Main outcomes of this study are presented in Table 1:

Table 1: Efficacy results for Monotherapy Study 310

	Zonisamide	**Carbamazepine**		
n (ITT population)*	281	300		
6-months seizure freedom* **			Diff	$CI_{95\%}$
PP-population**	79.4%	83.7%	-4.5%	-12.2% ; 3.1%
ITT-population	69.4%	74.7%	-6.1%	-13.6% ; 1.4%
≤ 4 seizures during 3 month baseline period	71.7%	75.7%	-4.0%	-11.7% ; 3.7%
> 4 seizures during 3 month baseline period	52.9%	68.9%	-15.9%	-37.5% ; 5.6%
12-months seizure freedom** **				
PP-population	67.6%	74.7%	-7.9%	- 17.2% ; 1.5%
ITT-population	55.9%	62.3%	-7.7%	- 16.1% ; 0.7%
≤ 4 seizures during 3 month baseline period	57.4%	64.7%	-7.2%	-15.7% ; 1.3%
> 4 seizures during 3 month baseline period	44.1%	48.9%	-4.8%	-26.9% ; 17.4%
Seizure sub-type (6-month seizure freedom-PP population)				
All partial	76.4%	86.0%	-9.6%	-19.2% ; 0.0%
Simple partial	72.3%	75.0%	-2.7%	-20.0% ; 14.7%
Complex partial	76.9%	93.0%	-16.1%	-26.3% ; -5.9%
All generalized Tonic-Clonic	78.9%	81.6%	-2.8	-11.5% ; 6.0%
Secondary Tonic-Clonic	77.4%	80.0%	-2.6%	-12.4% ; 7.1%
Generalized Tonic-Clonic	85.7%	92.0%	-6.3%	-23.1% ; 10.5%

PP = Per Protocol Population; ITT = Intent To Treat Population
*Two subjects withdrew consent after randomization and before taking study medication. The Safety Population therefore comprised 581 subjects.
**Primary endpoint.
***6-month seizure freedom: Proportion of subjects seizure free for 26 weeks.
****12-month seizure freedom: Proportion of subjects seizure free for 52 weeks.

Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation in adults

In adults, efficacy has been demonstrated with zonisamide in 4 double-blind, placebo-controlled studies of periods of up to 24 weeks with either once or twice daily dosing. These studies show that the median reduction in partial seizure frequency is related to zonisamide dose with sustained efficacy at doses of 300-500 mg per day.

The pivotal clinical study was a double-blind, placebo controlled randomised, parallel group study conducted at 54 sites in 19 countries comparing zonisamide at 100 mg (n= 56), at 300 mg (n=55), at 500 mg (n=118) and placebo (n= 120). After a prospective baseline period of 12 weeks, patients were randomised to one of the four treatment groups above. The treatment period consisted of a 6 week up-titration period and a 2 week stabilisation period followed by a 16 week fixed dose evaluation period, during which concomitant anti epileptic drug regimens were held constant. Patients then underwent 4 week down titration period or were included in an open label extension of the study.

The primary measure of effectiveness was the median percent reduction in seizure frequency from baseline. Secondary outcomes included the percentage of responders (patients with a greater than 50% reduction in seizure frequency from baseline). The results of the analyses of this study are provided in the tables below.

Table 2: Efficacy of zonisamide: seizure frequency (primary efficacy analysis population)

Treatment (weeks 19-36)	**Median % Reduction in Seizure Frequency from Baseline**			**Zonisamide-placebo Difference (with 95% CI) in Median % Reduction in Seizure Frequency from Baseline**		
	Complex partial seizures	**All partial seizures***	**All seizures****	**Complex partial seizures**	**All partial seizures***	**All seizures****
500 mg/day	51.2 (p<0.0001	50.6 (p<0.0001)	51.3 (p<0.0001)	-31.2 (-44.6,-15.7) (p<0.0001)	-27.3 (-38.9, -15.8) (p<0.0001)	-30.7 (-41.3, -19.6) (p<0.0001)
300 mg/day	40.1 (p=0.316)	46.4 (p=0.0007)	41.8 (p=0.0005)	-15.0 (-39.7, 12.6) (p=0.3160)	-26.9 (-42.3, -12.9) (p=0.0007)	-26.1 (-41.0,-12.5) (p=0.0005)
100 mg/day	11.4 (NA)	18.3 (p=0.7204)	18.6 (p=0.4452)	NA	-1.6 (-17.6, 11.5) (p=0.7204)	-5.8 (-20.3, 8.2) (p=0.4452)
Placebo	16.3	19.4	18.1	-	-	-

* All partial seizures without secondary generalization
** All partial and secondary generalized seizures
NA Not assessed
- Not applicable

Table 3: Efficacy of zonisamide: responders (primary efficacy analysis population)

Treatment (weeks 19-36)	Percentage of Responders* and Odds Ratio for Response (with 95% CI) **		
	Complex partial seizures	All partial seizures	All seizures***
500 mg/day	52.3 (p<0.001)	50.5 (p<0.001)	52.5 (p<0.001)
Odds Ratio 95% CI	4.01 (1.94-8.56) (p<0.001)	4.25 (2.02-8.95) (p<0.001)	4.63 (2.29-9.39) (p<0.001)
300 mg/day	36.0	42.9	42.2
100 mg/day	22.5	28.8	29.6
Placebo	21.3	20.2	17.9

* Responders are patients with ≥50% reduction in seizure frequency compared to baseline
** Odds ratios were only calculated for the 500 mg group
*** All partial and secondary generalized seizures

Indications

Zonisamide is indicated as:

- monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy who are intolerant to other agents or where other agents are contraindicated;
- adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

Contraindications

Hypersensitivity to zonisamide, to sulphonamides or any of the excipients.

Precautions

Suicidal Behaviour and Ideation

Antiepileptic drugs, including Zonegran, increase the risk of suicidal thoughts or behaviour 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 behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour 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 behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour 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 behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. 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 (5-100 years) in the clinical trials analysed.

Table 4 shows absolute and relative risk by indication for all evaluated AEDs.

Table 4: Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Zonegran or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to healthcare providers (see **Cognitive Adverse Events** subsection below).

Circumstances in which caution is required

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 medications once seizure control with zonisamide has been achieved in the add-on situation, in order to reach monotherapy with zonisamide. Therefore withdrawal of concomitant antiepileptic agents must be undertaken with caution.

Sulphonamide reactions

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.

Serious skin reactions

Serious rashes have occurred in association with zonisamide therapy, including isolated 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.

Serious haematological events

Isolated 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 and these events.

Metabolic acidosis

Zonisamide can cause metabolic acidosis, and by decreased of serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis and hyperchloremia and decreased serum bicarbonate. Metabolic acidosis is often asymptomatic.

Signs and symptoms of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia or more severe sequalae including cardiac arrhymias or stupor. The risk of development of zonisamide-induced metabolic acidosis appears to be greater at higher doses of zonisamide, but can occur with doses as low as 25 mg daily.

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 Zonegran 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.

The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in younger patients.

Data from one paediatric clinical trial shows a higher incidence of metabolic acidosis compared to data from trials of zonisamide in adults. Chronic metabolic acidosis in paediatric patients can reduce growth rates, resulting in a reduction in the maximal height achieved. The specific effects of zonisamide on growth and bone have not been investigated. 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.

Serum bicarbonate should be measured pre-treatment (baseline), on commencement of maintenance dosing, when dosage is increased and when strong CYP3A4 inhibitors are newly co-prescribed with zonisamide and at a minimum 6 monthly from the adoption of a maintenance regimen. Although acidosis has been demonstrated to be dose dependent it can present at any time. In addition, if signs or symptoms of metabolic acidosis are observed, serum bicarbonate should be measured. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Zonegran (by gradual discontinuation or reduction of a therapeutic dose) as osteopenia may develop. If the decision is made to continue patients on Zonegran in the face of persistent acidosis, alkali treatment should be considered.

Zonegran should be used with caution in patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate, as there are insufficient data to rule out a pharmacodynamic interaction.

Bicarbonate decrements are usually mild – moderate (average decrease of approximately 3.5 mEq/ L at daily doses of 300 mg in adults); rarely patients can experience more severe decrements. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or other drugs e.g acetazolamine) may be additive to the bicarbonate lowering effects of zonisamide. Therefore, combination of zonisamide with a ketogenic diet in the management of epilepsy is not advisable as it may increase the risk of metabolic acidosis.

Chronic, untreated metabolic acidosis may result in osteomalacia (referred to as rickets in paediatric patients) and/or osteoporosis with an increased risk for fractures. 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 (see Precautions, Laboratory Tests subsection).

Although the effects of metabolic acidosis from zonisamide on the fetus are not clearly known, metabolic acidosis in pregnancy (due to other causes) may affect fetal development (i.e., decreased fetal growth, decreased fetal oxygenation and fetal death) and the ability of the fetus to tolerate labour. In addition, significant amounts of zonisamide can appear in

the breast milk of nursing women taking zonisamide, and the effects of this exposure on the infant from metabolic acidosis, or any other cause, are unknown.

In a zonisamide monotherapy study (see section Adverse effects), the incidence of markedly abnormally low serum bicarbonate (a decrease to less than 17 mEq/l and by more than 5 mEq/l) was 3.8%. Reductions from baseline in serum bicarbonate of >3.5mmol/L occurred in 121/237 (51.1%) patients given zonisamide.

Kidney stones

Kidney stones have occurred in patients treated with zonisamide. In some cases, calculi were accompanied by urine abnormalities, hydronephrosis, haematuria, bladder stenosis or urinary tract infection. Zonisamide should be used with caution in patients who have risk factors for nephrolithiasis, including prior stone formation, a family history of nephrolithiasis and hypercalcuria. Such patients may be at increased risk of stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. In addition, patients taking other medications associated with nephrolithiasis may 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.

Among 991 patients treated during the development of Zonegran, 40 patients (4.0%) with epilepsy receiving Zonegran developed clinically possible or confirmed kidney stones (e.g. clinical symptomology, 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 detections. In nine patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonograph finding. The rate of occurrence of kidney stones was 28.7 per 1000 patient-years of exposure in the first six months, 62.6 per 1000 patients-years of exposure between 6 and 12 months, and 24.3 per 1000 patients-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. The analyzed stones were composed of calcium or urate salts.

Abnormal liver function tests

Findings not observed in clinical studies, but seen in the dog at exposure levels similar to clinical use, were liver changes (enlargement, dark-brown discoloration, mild hepatocyte enlargement with concentric lamellar bodies in the cytoplasm and cytoplasmic vacuolation) associated with increased metabolism.

Carbonic anhydrase inhibitors

Zonisamide should be used with caution in patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate, as there are insufficient data to rule out a pharmacodynamic interaction.

Oligohidrosis and hyperthermia

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. Most reports occurred during periods of warm weather. Patients or their carers must be warned to take care to maintain hydration and avoid exposure to excessive temperatures.

Caution should be used 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.

Muscle weakness

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.

Contraception

Women of child-bearing potential must use adequate contraception during treatment with zonisamide and for one month after discontinuation. Physicians treating patients with zonisamide should try to ensure that appropriate contraception is used, and should use clinical judgement when assessing whether oral contraceptives (OCs), or the doses of the OC components, are adequate based on the individual patient's clinical situation.

Allergic reactions

Zonegran 100 mg hard capsules contain a yellow colour called sunset yellow FCF (E110), which may cause allergic reactions.

Low body weight

There is limited data from clinical studies in patients with a body weight of less than 40 kg. Therefore these patients should be treated with caution.

Weight loss

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.

Discontinuation

No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child.

Cognitive adverse events

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 machinery.

Effects on fertility

The effect on human fertility is unknown. Rats treated orally with zonisamide before mating and during early gestation had reduced numbers of corpora lutea, implantations and live fetuses at a dose similar to the human therapeutic dose, on a mg/m^2 basis.

Use in pregnancy (Category D)

Zonisamide is teratogenic in mice, rats and dogs and embryolethal in monkeys when administered orally during the period of organogenesis. Administration to dogs was associated with increased incidences of fetal cardiovascular malformations (ventricular septal defects, cardiomegaly, valvular and arterial anomalies) at peak maternal plasma concentrations similar to those at the maximal recommended clinical dose. The incidence of skeletal malformations was also increased at peak maternal plasma concentrations of twice the maximal anticipated clinical concentration. Administration to cynomolgus monkeys was associated with increased incidences of embryofetal deaths at peak maternal plasma concentrations lower than the maximal anticipated clinical concentration. Administration to mice was associated with increased incidences of skeletal and/or craniofacial defects at doses similar to and greater than the maximal recommended clinical dose on a mg/m^2 basis. Administration to rats was associated with increased incidences of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, reduced skeletal ossification) at doses ranging from less than to greater than the maximal clinical dose on a mg/m^2 basis.

Oral administration to rats from late gestation to weaning was associated with delayed behavioural development at doses similar to the maximal clinical dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Zonisamide must not be used in pregnancy unless clearly necessary and only if the potential benefit is considered to justify the risk to the fetus. The need for antiepileptic treatment should be reviewed in patients planning to become pregnant. If zonisamide is prescribed, careful monitoring is recommended. Specialist advice should be given to women who are likely to become pregnant in order to consider the optimal treatment during pregnancy. Women of childbearing potential should be counselled to use contraception during treatment with zonisamide, and for one month after discontinuation.

Use in lactation

Zonisamide is excreted in human milk at a concentration similar to that in plasma. Oral administration of zonisamide to rats from late gestation to weaning was associated with delayed behavioural development at doses similar to the maximal clinical dose on a mg/m^2 basis. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from zonisamide therapy. 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.

Paediatric Use

The safety and efficacy of Zonegran in children under 18 years of age have not been established. The use of zonisamide in this age group is not recommended. Cases of oligohidrosis and hyperpyrexia have been reported. Zonisamide commonly causes metabolic acidosis in paediatric patients (see **Precautions, Metabolic acidosis subsection**). Chronic untreated metabolic acidosis in paediatric patients may cause nephrolithiasis and/or nephrocalcinosis, osteoporosis and/or osteomalacia (potentially decrease the maximal height achieved). The effect of zonisamide on growth and bone-related sequelae has not been systematically investigated.

Use in the 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 Adverse effects).

Genotoxicity

The genotoxicity of zonisamide has been studied in an adequate range of *in vitro* and *in vivo* assays, and the weight of evidence suggests that it is unlikely to cause genetic toxicity at therapeutic levels of exposure.

Carcinogenicity

Zonisamide did not display carcinogenic activity in lifetime studies in mice or rats following dietary administration at doses similar to the maximal recommended clinical dose on a mg/m^2 basis.

Effect on laboratory tests

Please refer to the warning under the metabolic acidosis heading in the section "Circumstances in which caution is required" regarding impact of zonisamide on bicarbonate levels.

Interactions with other medicines

Antiepileptic drugs

In epileptic patients, steady-state dosing with zonisamide resulted in no clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, or sodium valproate. The effect of zonisamide on phenobarbitone pharmacokinetics has not been studied.

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

There are insufficient data to rule out possible pharmacodynamic interactions with

carbonic anhydrase inhibitors such as topiramate. Patients taking a combination of carbonic anhydrase inhibitors may be at increased risk of metabolic acidosis and nephrolithiasis. These combinations are not recommended.

Potential medicinal product interactions affecting Zonegran

In clinical studies co-administration of lamotrigine had no apparent effect on zonisamide pharmacokinetics. The combination 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 antiepileptic 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.

Adverse effects

Zonegran has been administered to over 1,200 patients in clinical studies, more than 400 of whom received Zonegran for at least 1 year. In addition there has been extensive post-marketing experience with zonisamide in Japan since 1989 and in the USA since 2000.

Adverse Event Incidence in Controlled Clinical Trials

Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation in adults

The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia.

Table 5 lists treatment emergent adverse events occurring in ≥ 1% of zonisamide treated patients and greater than placebo.

Table 5 Treatment Emergent Adverse Events occurring in >/= 1% of Zonisamide treated patients and greater than placebo		
Body System and COSTART Preferred Term	**Number (%) of Subjects**	
	All Doses (N=498)	**Placebo (N=350)**
Any adverse event	388 (77.9)	237 (67.7)
Body as a whole		
Abdominal pain	36 (7.2)	12 (3.4)
Allergic Reaction	5 (1.0)	2 (0.6)
Flu syndrome	20 (4.0)	10 (2.9)
Pain	18 (3.6)	11 (3.1)
Viral Infection	7 (1.4)	4 (1.1)
Cardiovascular		
Vasodilatation	7 (1.4)	2 (0.6)
Digestive		
Anorexia	54 (10.8)	15 (4.3)
Constipation	14 (2.8)	4 (1.1)
Diarrhoea	29 (5.8)	13 (3.7)
Dry mouth	5 (1.0)	2 (0.6)
Dyspepsia	13 (2.6)	3 (0.9)
Nausea	48 (9.6)	28 (8.0)
Hematologic and Lymphatic		
Ecchymosis	11 (2.2)	3 (0.9)
Leukopenia	7 (1.4)	0 (0.0)
Metabolic and Nutritional		
Weight loss	20 (4.0)	6 (1.7)
Musculoskeletal		
Arthralgia	5 (1.0)	3 (0.9)
Myasthenia	5 (1.0)	1 (0.3)
Nervous system		
Abnormal gait	13 (2.6)	5 (1.4)
Agitation/irritability	37 (7.4)	17 (4.9)
Altered cognitive function	78 (15.7)	23 (6.6)
Anxiety	19 (3.8)	11 (3.1)
Ataxia	28 (5.6)	8 (2.3)
CNS depression	141 (28.3)	65 (18.6)
Confusion	28 (5.6)	9 (2.6)
Depression	31 (6.2)	10 (2.9)

Table 5 Treatment Emergent Adverse Events occurring in >/= 1% of Zonisamide treated patients and greater than placebo		
Body System and COSTART Preferred Term	**Number (%) of Subjects**	
	All Doses (N=498)	**Placebo (N=350)**
Difficulty concentrating	32 (6.4)	7 (2.0)
Difficulty with memory	25 (5.0)	5 (1.4)
Dizziness	77 (15.5)	29 (8.3)
Emotional lability/moodiness	20 (4.0)	10 (2.9)
Fatigue	33 (6.6)	22 (6.3)
Hypesthesia	8 (1.6)	4 (1.1)
Incoordination	6 (1.2)	3 (0.9)
Insomnia	27 (5.4)	11 (3.1)
Mental slowing	15 (3.0)	7 (2.0)
Nervousness	9 (1.8)	3 (0.9)
Nystagmus	18 (3.6)	7 (2.0)
Paresthesia	16 (3.2)	6 (1.7)
Psychomotor slowing	8 (1.6)	3 (0.9)
Psychosis/Psychotic Disorder	5 (1.0)	3 (0.9)
Schizophrenic/Schizophreniform behaviour	7 (1.4)	2 (0.6)
Somnolence	80 (16.1)	29 (8.3)
Speech & Language abnormalities	29 (5.8)	6 (1.7)
Tiredness	43 (8.6)	24 (6.9)
Tremor	16 (3.2)	7 (2.0)
Renal and Urinary disorders		
Nephrolithiasis*	>1%	
Respiratory		
Cough increased	8 (1.6)	4 (1.1)
Pharyngitis	21 (4.2)	10 (2.9)
Rhinitis	8 (1.6)	4 (1.1)
Sinusitis	7 (1.4)	4 (1.1)
Skin and Appendages		
Acne	5 (1.0)	2 (0.6)
Rash	14 (2.8)	8 (2.3)
Sweating	5 (1.0)	1 (0.3)
Special senses		
Amblyopia	13 (2.6)	8 (2.3)

Table 5 Treatment Emergent Adverse Events occurring in >/= 1% of Zonisamide treated patients and greater than placebo		
Body System and COSTART Preferred Term	**Number (%) of Subjects**	
	All Doses (N=498)	**Placebo (N=350)**
Diplopia	35 (7.0)	13 (3.7)
Otitis media	6 (1.2)	1 (0.3)
Taste perversion	8 (1.6)	1 (0.3)
Tinnitus	5 (1.0)	3 (0.9)
Urogenital		
Urinary tract infection	10 (2.0)	6 (1.7)

*Note that the incidence of nephrolithiasis is based on the reported incidence in the open-label studies since it appears to increase in frequency with increased duration of therapy.

Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy

A monotherapy study conducted in 583 adult subjects with newly diagnosed partial seizures with or without secondary generalised tonic-clonic seizures showed that 60.5% in the zonisamide group and 61.7% in the carbamazepine prolonged release (PR) group experienced adverse effects. Serious adverse effects were experienced by 5.3% in the zonisamide group and 5.7% in the carbamazepine PR group. Subjects treated with zonisamide were more likely to experience loss of appetite (7.8% versus 1.7%) and weight loss (6.8% versus 0%); 13.2% of subjects lost ≥10% of their body weight, and 0.7% lost ≥20%.

There were more reports of psychiatric disorders (9.3% versus 4.7%), and fewer reports of dizziness (3.9% versus 7.7%) and rash (2.1% versus 4.3%) in subjects treated with zonisamide compared to those treated with carbamazepine PR.

Table 6: Treatment Emergent Adverse Events (by MedDRA System Organ Class and Preferred Term) occurring in ≥ 1% of Subjects in either Treatment Group in the Safety Population of the Pivotal Double-Blind, Active-Controlled, Monotherapy Study		
	Number (%) of Subjects	
MedDRA SOC Preferred Term	**Zonisamide-exposed subjects (N=281)**	**Carbamazepine-exposed subjects (N=300)**
Subjects with Any TEAE	**170 (60.5)**	**185 (61.7)**
Nervous System Disorders		
headache	29 (10.3)	37 (12.3)
somnolence	17 (6.0)	23 (7.7)
dizziness	11 (3.9)	23 (7.7)
memory impairment	8 (2.8)	8 (2.7)
paraesthesia	6 (2.1)	3 (1.0)

Table 6: Treatment Emergent Adverse Events (by MedDRA System Organ Class and Preferred Term) occurring in ≥ 1% of Subjects in either Treatment Group in the Safety Population of the Pivotal Double-Blind, Active-Controlled, Monotherapy Study

	Number (%) of Subjects	
MedDRA SOC Preferred Term	**Zonisamide-exposed subjects (N=281)**	**Carbamazepine-exposed subjects (N=300)**
disturbance in attention	6 (2.1)	2 (0.7)
partial seizures with secondary generalisation	1 (0.4)	5 (1.7)
aphasia	2 (0.7)	3 (1.0)
ataxia	3 (1.1)	1 (0.3)
myoclonus	0	3 (1.0)
Gastrointestinal disorders		
nausea	11 (3.9)	10 (3.3)
18iarrhea	10 (3.6)	9 (3.0)
constipation	7 (2.5)	7 (2.3)
vomiting	6 (2.1)	8 (2.7)
abdominal pain upper	2 (0.7)	5 (1.7)
dyspepsia	4 (1.4)	3 (1.0)
abdominal pain	2 (0.7)	4 (1.3)
gastritis	4 (1.4)	2 (0.7)
hyperchlorhydria	3 (1.1)	2 (0.7)
haemorrhoids	1 (0.4)	3 (1.0)
toothache	0	3 (1.0)
General disorders and administration site conditions		
fatigue	13 (4.6)	12 (4.0)
pyrexia	11 (3.9)	12 (4.0)
asthenia	5 (1.8)	7 (2.3)
gait disturbance	3 (1.1)	5 (1.7)
irritability	7 (2.5)	1 (0.3)
chest pain	0	5 (1.7)
pain	0	3 (1.0)
Infections and Infestations		
nasopharyngitis	10 (3.6)	6 (2.0)
upper respiratory tract infection	6 (2.1)	6 (2.0)
urinary tract infection	3 (1.1)	7 (2.3)
influenza	3 (1.1)	4 (1.3)
cystitis	1 (0.4)	4 (1.3)
rhinitis	3 (1.1)	2 (0.7)
viral infection	0	4 (1.3)
respiratory tract infection	0	3 (1.0)
Skin and subcutaneous tissue disorders		
rash	6 (2.1)	13 (4.3)
dermatitis allergic	1 (0.4)	5 (1.7)
alopecia	3 (1.1)	2 (0.7)
Investigations		
weight decreased	19 (6.8)	0
alanine aminotransferase increased	3 (1.1)	6 (2.0)
aspartate aminotransferase increased	2 (0.7)	4 (1.3)
blood creatine phosphokinase increased	3 (1.1)	2 (0.7)
weight increased	1 (0.4)	4 (1.3)
blood urine present	3 (1.1)	0

Table 6: Treatment Emergent Adverse Events (by MedDRA System Organ Class and Preferred Term) occurring in ≥ 1% of Subjects in either Treatment Group in the Safety Population of the Pivotal Double-Blind, Active-Controlled, Monotherapy Study

	Number (%) of Subjects	
MedDRA SOC Preferred Term	**Zonisamide-exposed subjects (N=281)**	**Carbamazepine-exposed subjects (N=300)**
Psychiatric disorders		
depression	6 (2.1)	5 (1.7)
anxiety	5 (1.8)	3 (1.0)
insomnia	6 (2.1)	1 (0.3)
agitation	3 (1.1)	0
bradyphrenia	3 (1.1)	0
mood swings	3 (1.1)	0
sleep disorder	3 (1.1)	0
Metabolism and nutrition disorders		
decreased appetite	22 (7.8)	5 (1.7)
Musculoskeletal and connective tissue disorders		
back pain	5 (1.8)	4 (1.3)
arthralgia	3 (1.1)	2 (0.7)
pain in extremity	1 (0.4)	3 (1.0)
musculoskeletal pain	0	3 (1.0)
Respiratory, thoracic and mediastinal disorders		
oropharyngeal pain	4 (1.4)	4 (1.3)
cough	3 (1.1)	2 (0.7)
epistaxis	4 (1.4)	1 (0.3)
Vascular disorders		
hypertension	5 (1.8)	8 (2.7)
Ear and labyrinth disorders		
vertigo	5 (1.8)	10 (3.3)
Blood and lymphatic system disorders		
eosinophilia	4 (1.4)	2 (0.7)
Cardiac disorders		
bradycardia	3 (1.1)	1 (0.3)
Renal and urinary disorders		
haematuria	0	3 (1.0)
Eye disorders		
vision blurred	5 (1.8)	1 (0.3)

MedDRA = Medical Dictionary for Regulatory Activities, SOC = System Organ Class,

Other adverse reactions associated with zonisamide obtained from clinical studies and post-marketing surveillance and occurring in less than 1% of zonisamide treated patients is included in Table 7 below.

The frequencies are arranged according to the following scheme:

uncommon	> 1/1,000 < 1/100
rare	> 1/10,000 < 1/1,000
very rare	< 1/10,000 including isolated reports

Table 7: Treatment Emergent Adverse Reactions occurring in </= 1% of Zonisamide treated patients		
System Organ Class (MedDRA terminology)	**Uncommon**	**Very Rare**
Blood and Lymphatic system disorders		Agranulocytosis Aplastic anemia Thrombocytopenia
Immune system disorders	Hypersensitivity	
Psychiatric disorders	Suicide attempt	
Nervous system disorders		Status epilepticus
Gastrointestinal disorders		Pancreatitis
Skin and subcutaneous disorders		Anhidrosis Erythema multiforme Stevens-Johnson syndrome
Renal and urinary disorders		Renal failure
General disorders and administration site conditions		Hyperthermia Sudden unexplained death in epilepsy
Investigations		Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine phosphokinase increased Blood creatine increased Blood urea increased

Dosage and administration

Zonegran capsules are for oral use.

Dosage

Adults

Zonegran may be taken as monotherapy or added to existing therapy in adults. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 8. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

Table 8: Adults – recommended dosage escalation and maintenance regimen

Treatment Regimen	**Titration Phase**			**Usual Maintenance Dose**
Monotherapy - Newly diagnosed adult patients	**Week 1 + 2**	**Week 3 + 4**	**Week 5 + 6**	300 mg per 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.
	100 mg/day (once a day)	200 mg /day (once a day)	300 mg / day (once a day)	
Adjunctive therapy - with CYP3A4-inducing agents (see section 4.5)	**Week 1**	**Week 2**	**Week 3 to 5**	300 to 500 mg per day (once a day or two divided doses).
	50 mg/day (in two divided doses)	100 mg /day (in two divided doses)	Increase at weekly intervals in increments of 100 mg	
- without CYP3A4-inducing agents; or with renal or hepatic impairment	**Week 1 + 2**	**Week 3 + 4**	**Week 5 to 10**	300 to 500 mg per day (once a day or two divided doses). Some patients may respond to lower doses.
	50 mg/day (in two divided doses)	100 mg / day (in two divided doses)	Increase at two-weekly intervals in increments of up to 100 mg	

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 Adverse effects).

Paediatric Use

The safety and efficacy in children and adolescents under 18 years have not been established. Therefore use in these patients is not recommended (refer to Paediatric Use)

Dosage adjustment in renal insufficiency

Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients and a 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.

Dosage adjustment in hepatic insufficiency

Use 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.

Dosage adjustment in Dialysis

Use in patients undergoing dialysis has not been studied.

Dosage adjustment in concomitant disease.

Refer to information provided for dosage adjustment in renal and hepatic insufficiency.

Maximum tolerated daily dose and the maximum dose for an entire course of therapy.

Although in some studies higher doses were used, the maximum recommended daily dose is 500 mg.

There is no recommended maximum dose for an entire course of therapy.

Monitoring advice.

Effect of food

Zonisamide may be taken with or without food.

Withdrawal of zonisamide

When zonisamide treatment is to be discontinued, it should be withdrawn gradually (see section Circumstances in which caution is required). In clinical studies of adult patients, dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic drug doses (where necessary).

Overdosage

There have been cases of accidental and intentional overdose in adult and paediatric patients. In some cases, the overdoses were asymptomatic, whereas in other cases the overdose was followed by symptoms such as somnolence, nausea, gastritis, nystagmus, myoclonus, coma, bradycardia, reduced renal function, hypotension and respiratory depression. A very high plasma concentration of 100.1 μg/ml zonisamide was recorded approximately 31 hours after a patient took an overdose of zonisamide and clonazepam; the patient became comatose and had respiratory depression, but recovered consciousness five days later and had no sequelae.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage

Treatment

No specific antidotes for zonisamide overdose are available. General supportive care is indicated, including frequent monitoring of vital signs and close observation. Zonisamide has a long elimination half-life so its effects 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.

Presentation and storage conditions

Presentation of the medicine

Zonegran 25 mg (AUST R 125869) is available in blister packs of 14 and 56 hard capsules with white opaque body and white opaque cap marked with a logo and "ZONEGRAN 25" in black ink.

Zonegran 50 mg (AUST R 125870) is available in blister packs of 56 hard capsules with white opaque body and grey opaque cap marked with a logo and "ZONEGRAN 50" in black ink.

Zonegran 100 mg (AUST R 125871) is available in blister packs of 56 hard capsules with white opaque body and red opaque cap marked with a logo and "ZONEGRAN 100" in black ink.

Storage conditions

Store below 25°C.

Name and address of the sponsor

SciGen (Australia) Pty Ltd
Suite 1, 13b Narabang Way
Belrose NSW 2085
Australia

Telephone: 1800 966 303

Poisons Schedule of the medicine

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

7 June 2007

Date of most recent amendment

04 April 2013