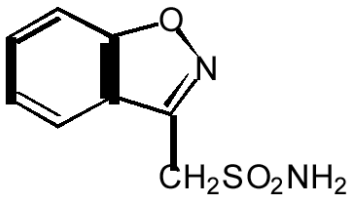
ZONEGRAN® (zonisamide) capsules Rx Only

DESCRIPTION

ZONEGRAN® (zonisamide) is an antiseizure drug chemically classified as a sulfonamide and unrelated to other antiseizure agents. The active ingredient is zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. The empirical formula is $C_8H_8N_2O_3S$ with a molecular weight of 212.23. Zonisamide is a white powder, pKa = 10.2, and is moderately soluble in water (0.80 mg/mL) and 0.1 N HCl (0.50 mg/mL).

The chemical structure is:



ZONEGRAN is supplied for oral administration as capsules containing 25 mg or 100 mg zonisamide. Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

CLINICAL PHARMACOLOGY

Mechanism of Action: The precise mechanism(s) by which zonisamide exerts its antiseizure effect is unknown. Zonisamide demonstrated anticonvulsant activity in several experimental models. In animals, zonisamide was effective against tonic extension seizures induced by maximal electroshock but ineffective against clonic seizures induced by subcutaneous pentylenetetrazol. Zonisamide raised the threshold for generalized seizures in the kindled rat model and reduced the duration of cortical focal seizures induced by electrical stimulation of the visual cortex in cats. Furthermore, zonisamide suppressed both interictal spikes and the secondarily generalized seizures produced by cortical application of tungstic acid gel in rats or by cortical freezing in cats. The relevance of these models to human epilepsy is unknown.

Zonisamide may produce these effects through action at sodium and calcium channels. *In vitro* pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca^{2+} currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. *In vitro* binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion which does not produce changes in chloride flux. Other *in vitro* studies have demonstrated that zonisamide (10–30 µg/mL) suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons) or neuronal or glial uptake of [^{3}H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. *In vivo* microdialysis studies demonstrated that zonisamide facilitates both dopaminergic and serotonergic neurotransmission. Zonisamide also has weak carbonic

anhydrase inhibiting activity, but this pharmacologic effect is not thought to be a major contributing factor in the antiseizure activity of zonisamide.

Pharmacokinetics: Following a 200–400 mg oral zonisamide dose, peak plasma concentrations (range: 2–5 µg/mL) in normal volunteers occur within 2–6 hours. In the presence of food, the time to maximum concentration is delayed, occurring at 4–6 hours, but food has no effect on the bioavailability of zonisamide. Zonisamide extensively binds to erythrocytes, resulting in an eight-fold higher concentration of zonisamide in red blood cells (RBC) than in plasma. The pharmacokinetics of zonisamide are dose proportional in the range of 200–400 mg, but the C_{max} and AUC increase disproportionately at 800 mg, perhaps due to saturable binding of zonisamide to RBC. Once a stable dose is reached, steady state is achieved within 14 days. The elimination half-life of zonisamide in plasma is about 63 hours. The elimination half-life of zonisamide in RBC is approximately 105 hours.

The apparent volume of distribution (V/F) of zonisamide is about 1.45 L/kg following a 400 mg oral dose. Zonisamide, at concentrations of 1.0–7.0 µg/mL, is approximately 40% bound to human plasma proteins. Protein binding of zonisamide is unaffected in the presence of therapeutic concentrations of phenytoin, phenobarbital or carbamazepine.

Metabolism and Excretion: Following oral administration of ^{14}C-zonisamide to healthy volunteers, only zonisamide was detected in plasma. Zonisamide is excreted primarily in urine as parent drug and as the glucuronide of a metabolite. Following multiple dosing, 62% of the ^{14}C dose was recovered in the urine, with 3% in the feces by day 10. Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction to form the open ring metabolite, 2–sulfamoylacetyl phenol (SMAP). Of the excreted dose, 35% was recovered as zonisamide, 15% as N-acetyl zonisamide, and 50% as the glucuronide of SMAP. Reduction of zonisamide to SMAP is mediated by cytochrome P450 isozyme 3A4 (CYP3A4). Zonisamide does not induce its own metabolism. Plasma clearance of zonisamide is approximately 0.30–0.35 mL/min/kg in patients not receiving enzyme-inducing antiepilepsy drugs (AEDs). The clearance of zonisamide is increased to 0.5 mL/min/kg in patients concurrently on enzyme-inducing AEDs.

Renal clearance is about 3.5 mL/min. The clearance of an oral dose of zonisamide from RBC is 2 mL/min.

Special Populations:

> **Renal Insufficiency:** Single 300 mg zonisamide doses were administered to three groups of volunteers. Group 1 was a healthy group with a creatinine clearance ranging from 70–152 mL/min. Group 2 and Group 3 had creatinine clearances ranging from 14.5–59 mL/min and 10–20 mL/min, respectively. Zonisamide renal clearance decreased with decreasing renal function (3.42, 2.50, 2.23 mL/min, respectively). Marked renal impairment (creatinine clearance < 20 mL/min) was associated with an increase in zonisamide AUC of 35% (see **DOSAGE AND ADMINISTRATION** section).

Hepatic Disease: The pharmacokinetics of zonisamide in patients with impaired liver function have not been studied (see DOSAGE AND ADMINISTRATION section).

Age: The pharmacokinetics of a 300 mg single dose of zonisamide was similar in young (mean age 28 years) and elderly subjects (mean age 69 years).

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

Interactions of Zonisamide with Other Antiepilepsy Drugs (AEDs): Concurrent medication with drugs that either induce or inhibit CYP3A4 may alter serum concentrations of zonisamide. Concomitant administration of phenytoin and carbamazepine increases zonisamide plasma clearance from 0.30-0.35 mL/min/kg to 0.35–0.5 mL/min/kg. The half-life of zonisamide is decreased to 27 hours by phenytoin, to 38 hours by phenobarbital and carbamazepine, and to 46 hours by valproate. Plasma protein binding of phenytoin and carbamazepine was not affected by zonisamide administration (see **PRECAUTIONS, Drug Interactions** subsection).

Clinical Studies: The effectiveness of ZONEGRAN as adjunctive therapy (added to other antiepilepsy drugs) has been established in three multicenter, placebo-controlled, double blind, 3-month clinical trials (two domestic, one European) in 499 patients with refractory partial onset seizures with or without secondary generalization. Each patient had a history of at least four partial onset seizures per month in spite of receiving one or two antiepilepsy drugs at therapeutic concentrations. The 499 patients (209 women, 290 men) ranged in age from 13–68 years with a mean age of about 35 years. In the two US studies, over 80% of patients were Caucasian; 100% of patients in the European study were Caucasian. ZONEGRAN or placebo was added to the existing therapy. The primary measure of effectiveness was median percent reduction from baseline in partial seizure frequency. The secondary measure was proportion of patients achieving a 50% or greater seizure reduction from baseline (responders). The results described below are for all partial seizures in the intent-to-treat populations.

In the first study (n = 203), all patients had a 1-month baseline observation period, then received placebo or ZONEGRAN in one of two dose escalation regimens; either 1) 100 mg/day for five weeks, 200 mg/day for one week, 300 mg/day for one week, and then 400 mg/day for five weeks; or 2) 100 mg/day for one week, followed by 200 mg/day for five weeks, then 300 mg/day for one week, then 400 mg/day for five weeks. This design allowed a 100 mg vs. placebo comparison over weeks 1–5, and a 200 mg vs. placebo comparison over weeks 2–6; the primary comparison was 400 mg (both escalation groups combined) vs. placebo over weeks 8–12. The total daily dose was given as twice a day dosing. Statistically significant treatment differences favoring ZONEGRAN were seen for doses of 100, 200, and 400 mg/day.

In the second (n = 152) and third (n = 138) studies, patients had a 2–3 month baseline, then were randomly assigned to placebo or ZONEGRAN for three months. ZONEGRAN was introduced by administering 100 mg/day for the first week, 200 mg/day the second week, then 400 mg/day for two weeks, after which the dose (ZONEGRAN or placebo) could be

adjusted as necessary to a maximum dose of 20 mg/kg/day or a maximum plasma level of 40 µg/mL. In the second study, the total daily dose was given as twice a day dosing; in the third study, it was given as a single daily dose. The average final maintenance doses received in the studies were 530 and 430 mg/day in the second and third studies, respectively. Both studies demonstrated statistically significant differences favoring ZONEGRAN for doses of 400–600 mg/day, and there was no apparent difference between once daily and twice daily dosing (in different studies). Analysis of the data (first 4 weeks) during titration demonstrated statistically significant differences favoring ZONEGRAN at doses between 100 and 400 mg/day. The primary comparison in both trials was for any dose over Weeks 5–12.

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

Study	Median % reduction in partial seizures		% Responders	
	ZONEGRAN	Placebo	ZONEGRAN	Placebo
Study 1:	n=98	n=72	n=98	n=72
Weeks 8-12:	40.5%*	9.0%	41.8%*	22.2%
Study 2:	n=69	n=72	n=69	n=72
Weeks 5-12:	29.6%*	-3.2%	29.0%	15.0%
Study 3:	n=67	n=66	n=67	n=66
Weeks 5-12:	27.2%*	-1.1%	28.0%*	12.0%

* p<0.05 compared to placebo

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

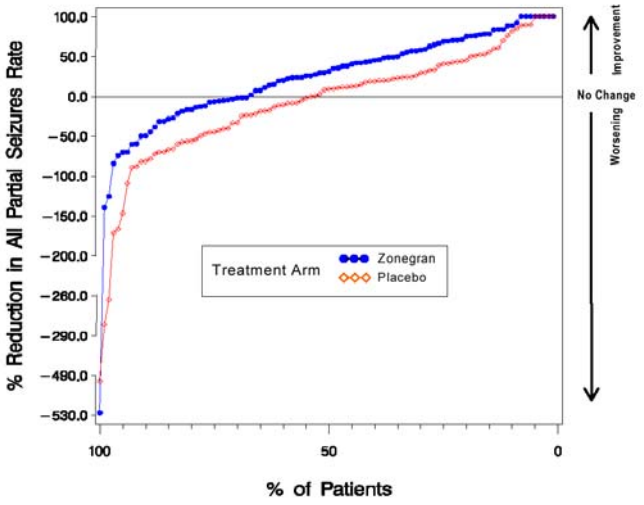
Dose Group	Median % reduction in partial seizures		% Responders	
	ZONEGRAN	Placebo	ZONEGRAN	Placebo
100-400 mg/day:	n=112	n=83	n=112	n=83
Weeks 1-12:	32.3%*	5.6%	32.1%*	9.6%
100 mg/day:	n=56	n=80	n=56	n=80
Weeks 1-5:	24.7%*	8.3%	25.0%*	11.3%
200 mg/day:	n=55	n=82	n=55	n=82
Weeks 2-6:	20.4%*	4.0%	25.5%*	9.8%

* p<0.05 compared to placebo

Figure 1 presents the proportion of patients (X-axis) whose percentage reduction from baseline in the all partial seizure rate was at least as great as that indicated on the Y-axis in the second and third placebo-controlled trials. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in seizure rate), while a negative value indicates a worsening from baseline (i.e., an increase in seizure rate). Thus, in a display of this type,

the curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure rate was consistently higher for the ZONEGRAN groups compared to the placebo groups. For example, Figure 1 indicates that approximately 27% of patients treated with ZONEGRAN experienced a 75% or greater reduction, compared to approximately 12% in the placebo groups.

Figure 1 Proportion of Patients Achieving Differing Levels of Seizure Reduction in ZONEGRAN and Placebo Groups in Studies 2 and 3



No differences in efficacy based on age, sex or race, as measured by a change in seizure frequency from baseline, were detected.

INDICATIONS AND USAGE

ZONEGRAN is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

CONTRAINDICATIONS

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

WARNINGS

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

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