The following is an English translation of the package insert for the drug sold in Japan (as of October 2014).

Prepared: October 2014

[**Antiepileptic Drug for Dogs**]

Veterinary drug, Powerful drug, Prescription legend drug

CONSAVE® Tablet 25 mg
CONSAVE® Tablet 100 mg

Zonisamide Tablet

CONSAVE®

®Trademark

CONSAVE Tablet is a novel antiepileptic drug developed by DS Pharma Animal Health Co., Ltd. The active ingredient, zonisamide, is a compound that has a sulfonamide structure and a benzisoxazole basic structure that was synthesized and developed by Sumitomo Dainippon Pharma Co., Ltd. Therapeutic efficacy and pharmacological studies have shown that zonisamide has an anticonvulsant effect. In clinical studies, the efficacy of zonisamide has been demonstrated for the treatment of idiopathic epilepsy in dogs and no clinically relevant safety findings have been reported.

■Composition

CONSAVE Tablet 25 mg contains 25 mg of zonisamide per tablet.
CONSAVE Tablet 100 mg contains 100 mg of zonisamide per tablet.

■Indications

Dogs: Control of partial seizures (including secondarily generalized seizures) and generalized seizures in idiopathic epilepsy

■Dosage and Administration

For oral use, the usual initial dosage of CONSAVE is 2.5 to 5 mg of zonisamide per kilogram of body weight administered 2 times daily approximately 12 hours apart. The dosage may be adjusted according to the dog's clinical signs; however, in principle, any increase in dose should not exceed 10 mg/kg/dose.

Initial dose by body weight:

Body weight	25 mg tablet	100 mg tablet	Dose (mg/kg/dose)
≥ 1.25 kg and < 2.5 kg	1/4 tablets		2.5 to 5.0
≥ 2.5 kg and < 5 kg	1/2 tablets		2.5 to 5.0
≥ 5 kg and < 10 kg	1 tablet		2.5 to 5.0
≥ 10 kg and < 20 kg		1/2 tablets	2.5 to 5.0
≥ 20 kg and < 40 kg		1 tablet	2.5 to 5.0
≥ 40 kg and < 80 kg		2 tablets	2.5 to 5.0

■Precautions

[General Precautions]

(1) CONSAVE Tablet is a prescription legend drug for use as prescribed and instructed by a licensed veterinarian.
(2) Since teratogenic effects have been suggested in humans and experimental animals in reports using zonisamide, caution should be exercised when handling the drug. A licensed veterinarian must inform pet owners of this risk.
(3) CONSAVE Tablets should only be used as stated in the Indications section.
(4) CONSAVE Tablets should only be used as indicated under Dosage and Administration.

[User Precautions]

(1) Consult a physician immediately if the drug is accidentally ingested by humans.
(2) Since congenital malformation has been reported in infants of female patients who received zonisamide preparations for human use during pregnancy, special precautions for accidental ingestion are required for women suspected of being pregnant or pregnant women.
(3) Infants should not handle CONSAVE Tablets.
(4) Since zonisamide is excreted in the urine of dogs receiving CONSAVE Tablets, the urine should be handled appropriately, and the user's hands washed after handling the urine.

[Precautions for Dogs]

1. Restrictions

(1) The maximum number of days for a single prescription is recommended to be approximately 1 month.
(2) Do not administer CONSAVE Tablets to dogs that are younger than 6 months old.
(3) Do not administer CONSAVE Tablets to pregnant or lactating dogs. Reproductive and developmental toxicity studies for dogs have reported anomalies of heart and great vessels (e.g. ventricular septal defects, overriding aorta, aortic stenosis), splenic abnormalities, and sternal abnormalities at a dose of 30 mg/kg/day, and fetal death, tail abnormalities, and thymic abnormalities at a dose of 60 mg/kg/day.
(4) CONSAVE Tablets should be administered with caution to dogs with suspected liver or renal disorders.
(5) CONSAVE Tablets should not be administered to dogs with a medical history of symptoms of hypersensitivity (e.g. rash/redness, pruritus).
(6) During CONSAVE Tablet use, blood concentration monitoring is recommended for appropriate dose adjustment. The target trough blood concentration should be between 10 and 40 μg/mL. Blood concentration should be monitored at the initial dose and approximately 1 week after dose changes, and, if the dog's condition is stable, periodical measurements (every 6 months) are recommended.
(7) Since status epilepticus may result from rapid dose reduction or discontinuation of dosing during repeated administration of CONSAVE Tablets, administration should be discontinued carefully through a gradual dose reduction.
(8) If epileptic seizures remain uncontrolled despite the blood concentration of the drug being within the therapeutic range after a dose increase of CONSAVE Tablets up to 10

mg/kg/dose, further dose increases should be avoided, and other antiepileptic drug should be added or CONSAVE Tablet should be switched to another antiepileptic drug. The maximum tolerated dose for CONSAVE Tablet is estimated to be 15 mg/kg/dose based on reports from safety studies or clinical studies; however, if the dose is increased to over 10 mg/kg/dose, the drug should be administered with caution after checking clinical signs and blood concentrations. If uncontrolled epileptic seizures are observed even after additional administration of other antiepileptic drugs or a change to another antiepileptic drug, prompt consultation with a licensed veterinarian who specializes in epilepsy treatment is required.

(9) For dogs using CONSAVE Tablets concomitantly with potassium bromide, seizure clusters have been reported to be caused by a decrease in blood concentration of potassium bromide in association with a change in diet. Since, in general, the drug disposition kinetics of potassium bromide is similar to that of sodium chloride, and the concentration of potassium bromide in body fluids is in equilibrium with the total amount of halogen, the absorption of potassium bromide is facilitated by a low salt diet and is adversely affected by a high salt diet. Therefore, if a dog receives potassium bromide, caution should be exercised for changes in diet.

(10) Since the efficacy of CONSAVE Tablets for drug-induced epilepsy has not been demonstrated, if a dog being treated with CONSAVE Tablets concomitantly receives a drug which may induce epilepsy, the appropriateness of such concomitant use should be carefully determined, regardless of administration of CONSAVE Tablets.

2. Adverse Reactions

(1) If an adverse reaction is observed in a dog, the dog should promptly undergo a medical examination by a licensed veterinarian.

(2) CONSAVE Tablet may cause vomiting, diarrhea, anorexia, and decreased activity. In such cases, appropriate corrective measures such as a dose reduction should be taken, as necessary.

(3) CONSAVE Tablet may cause symptoms of hypersensitivity (e.g. rash/redness, pruritus). In such cases, appropriate corrective measures such as discontinuation of CONSAVE Tablet should be taken, as necessary.

(4) If a high dose of CONSAVE Tablet is repeatedly administered, hepatic and renal function tests should be performed periodically, and treatment continued only if benefits outweigh risks.

(5) Since CONSAVE Tablet may cause anemia, a decrease in RBC and WBC, and a decrease in platelets, careful monitoring is required. In such cases, appropriate corrective measures such as discontinuation of CONSAVE Tablet should be taken, as necessary.

(6) Since zonisamide demonstrates weak carbonic anhydrase inhibitory activity (approximately one one-hundredth of acetazolamide), and CONSAVE Tablet may cause metabolic acidosis in association with a minor increase in blood chloride and a decrease in potassium, careful monitoring is required. In such cases, appropriate corrective measures such as discontinuation of CONSAVE Tablet should be taken, as necessary.

3. Interactions

(1) Zonisamide is primarily metabolized by CYP3A, a drug-metabolizing enzyme, in humans. A report has demonstrated that, in concomitant use with phenobarbital during repeated administration of zonisamide, enzymes induced by phenobarbital may decrease the blood concentration of zonisamide. Therefore, periodical monitoring of blood concentration of zonisamide after concomitant use with phenobarbital is also recommended. Similarly, for concomitant use of drugs that inhibit or induce the CYPs shown below, CONSAVE Tablets should be administered with caution because the blood concentration of zonisamide may increase or decrease.
CYP inhibitors: including erythromycin, clarithromycin, diltiazem, itraconazole, ketoconazole, miconazole, methylprednisolone, and cimetidine
CYP inducers: including omeprazole and dexamethasone

(2) During concomitant use of CONSAVE Tablets with drugs such as clomipramine, which are metabolized by monoamine oxidase (MAO) and MAO inhibitor drugs such as amitraz, the activity of these drugs may be enhanced due to the MAO inhibitory activity of CONSAVE Tablet. In such cases, special caution should be exercised during the administration of CONSAVE Tablets.

[Usage Precautions]

(1) Splitting CONSAVE Tablets should be performed at an appropriate location in a hospital by a licensed veterinarian or hospital staff instructed by a licensed veterinarian. If the tablet is split into 4 parts, an appropriate device such as a pill cutter should be used to cut the tablet into equal portions.

(2) CONSAVE Tablets should be discarded carefully to avoid pollution to the environment or water system, in accordance with regulations specified by local authorities.

[Storage Precautions]

(1) CONSAVE Tablets should be stored in an area that is inaccessible to children.

(2) CONSAVE Tablets should not be repacked into another container to avoid misuse and to preserve the quality of the drug.

[Other Precautions]

(1) Approximately 5 days are required for CONSAVE Tablet to exert maximum efficacy.

(2) The blood concentration of this drug varies among dogs for reasons such as individual differences; in particular, larger dogs tend to have higher blood concentration.

(3) The response rate of CONSAVE Tablet against epileptic seizures by seizure type in clinical studies was 79.4% for generalized seizures, 71.4% for partial seizures (except secondarily generalized seizures), and 57.1% for secondarily generalized seizures that develop from partial seizures.

(4) Although no serious adverse reactions have been reported in studies (clinical studies or safety studies) in which dogs received CONSAVE Tablets, the following serious adverse reactions are listed in the package inserts of drugs for human use which contain zonisamide as an effective ingredient: oculomucocutaneous syndrome (Stevens-Johnson syndrome), hypersensitivity syndrome, aplastic anemia, agranulocytosis, aplasia pure red cell, thrombocytopenia, acute renal failure, interstitial pneumonia, hepatic dysfunction, jaundice, rhabdomyolysis, calculus kidney/urinary, heat illness associated with decreased sweating, neuroleptic malignant syndrome (syndrome malin), hallucination, and delusion.

■Therapeutic Efficacy and Pharmacology

CONSAVE Tablet showed suppressive effects during the tonic extensor convulsion phase in maximal electroshock seizure models (mouse, rat, rabbit, and dog) and pentylenetetrazol-induced seizure models (mouse). Although the mechanism of action is still not completely

understood, previous studies have suggested that, in addition to decreased nerve cell overactivity through the blockage of voltage-dependent Na^+ channels, excessive synchronous excitation of nerve cells are suppressed in association with stabilized nerve cell membranes through the blockage of voltage-dependent T-type Ca^{2+} channels.
Suppression of glutamate release is reported as an additional mechanism of action, which is caused by controlled reuptake of neurotransmitters through the upregulation of excitatory amino acid transporter-1 and downregulation of GABA transporter-1, and through the indirect block of ryanodine receptors on excessive excitatory neurons. Moreover, free radical scavenging activity is also expected as a neuroprotective effect.

■*In Vivo* Pharmacokinetics

1. Blood Concentration

After administration of [^{14}C]zonisamide to dogs, the blood concentration of zonisamide quickly increased and reached a peak value within 3 hours after administration, thereafter gradually disappearing with a $t_{1/2}$ of 15 hours.
During repeated administration of zonisamide to dogs at a dose of 5 or 10 mg/kg/dose twice daily or 30 mg/kg/dose once daily, the blood concentration of zonisamide reached the steady state approximately 5 days after administration of each dose, and mean trough concentration was approximately 12 µg/mL for the dose of 5 mg, 27 µg/mL for the dose of 10 mg, and 40 µg/mL for the dose of 30 mg. AUC and C_{max} in repeated administrations increased to 2 to 3 times the values observed after the initial dose. A linear correlation was found between daily doses (up to 30 mg/kg/day) and plasma exposure-doses.

2. Distribution in Tissues

After oral administration of [^{14}C]zonisamide to rats, the tissue concentration peaked after 3 hours after administration, and was 1/2 to 2 times the blood concentration in most tissues, including the central nervous system, showing a tendency for uniform distribution to the whole body. Ninety-six hours after administration, radioactivity disappeared or decreased to 0.6 µg equivalent/g or lower; however, relatively high concentrations of 1.3 µg equivalent/mL was noted only in RBCs.

3. Metabolism

After administering a single oral dose of [^{14}C]zonisamide at 20 mg/kg/dose to dogs, unchanged zonisamide was excreted in urine as the major component of urinary metabolism (14.2%). A small amount of metabolites were also identified in urine: glucuronic acid conjugated zonisamide (0.5%), glucuronic acid conjugated zonisamide with a ring-opened isoxazole(2.2%), and glucuronic acid conjugated zonisamide with a hydroxylated benzene-ring (2.9%).

4. Excretion

After administration of a single oral dose of [^{14}C]zonisamide at 20 mg/kg/dose to dogs, 83% of administrated zonisamide was excreted into urine and the remaining (17%) was excreted into feces within 72 hours.

■Safety

1. Subacute Toxicity

To evaluate subacute toxicity, zonisamide was forcedly administered orally to dogs at a dose of 10, 30, and 100 mg/kg/dose once daily 6 days a week for 2 months. The results demonstrated that the no-observed-effect level was 10 mg/kg/day. Minimal effects on the stomach, liver, and kidney were observed in dogs that received zonisamide at a dose of 30 or 100 mg/kg/day.

2. Chronic Toxicity

To evaluate chronic toxicity, zonisamide was forcedly orally administered to dogs at a dose of 10, 30, and 75 mg/kg/dose once daily 7 days a week for 52 weeks. The results demonstrated a decrease in food intake observed in 1 dog at a dose of 30 mg/kg/day. In dogs receiving a dose of 75 mg/kg/day, weight loss, decrease in food intake, blood alkaline phosphatase increased, albumin decreased, and a tendency for increased liver weight and kidney weight were observed, and hepatocyte swelling/vacuolation and bladder congestion were observed in histopathological examinations. From the above results, the no-observed-adverse effect level was considered as 10 mg/kg/day and the toxic level was considered 30 mg/kg/day. Since, in general, the dose of antiepileptic drugs is increased close to the maximum tolerated dose to verify the efficacy of the drug, the maximum tolerated dose was estimated to be 30 mg/kg/day, the dose at which mild toxicity was observed.

3. Teratogenic Effects

Zonisamide was orally administered to female rats at doses of 20, 60, and 200 mg/kg/day, to mice at doses of 125, 250, and 500 mg/kg/day, to dogs at doses of 10, 30, and 60 mg/kg/day, and to monkeys at doses of 10 and 20 mg/kg/day. The following abnormalities were observed in fetuses: weight loss and delayed ossification at a dose of 60 mg/kg/day, and residual thymus in the cervical region and ventricular septal defects at a dose of 200 mg/kg/day in rats; delayed ossification at a dose of 250 mg/kg/day, and weight loss, cleft palate, open eyelid, cerebral ventricle dilatation, renal pelvis dilatation, and abnormalities in the thoracic vertebrae, ribs, and sternum at a dose of 500 mg/kg/day in mice; and weight loss, anomalies of heart and great vessels such as ventricular septal defects, overriding aorta, and coarctation of the aorta, splenic hypoplasia or dysplasia, and abnormalities in the sternum at a dose of 30 mg/kg/day, and fetal death, abnormalities in the tail, and thymic hypoplasia or dysplasia at a dose of 60 mg/kg/day in dogs. In monkeys, abortion was observed at a dose of 10 mg/kg/day and fetal death was observed at a dose of 20 mg/kg/day; however, the development of a living fetus was not affected and a teratogenic effect was not observed.

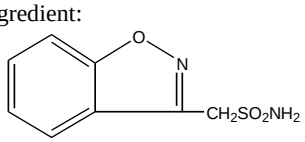
4. Risk in Humans

Congenital malformations (such as ventricular septal defects and atrial septal defects) have been reported in infants of female patients who received zonisamide preparations for human use during pregnancy.

■Description

CONSAVE Tablet 25 mg is a white to yellowish white, scored uncoated tablet. The diameter of the tablet is approximately 6 mm.
CONSAVE Tablet 100 mg is a white to yellowish white, scored uncoated tablet. The diameter of the tablet is approximately 9 mm.

Effective Ingredient:



Generic name: Zonisamide
Chemical name: 1,2-benzisoxazole-3-methanesulfonamide
Molecular formula: $C_8H_8N_2O_3S$
Molecular weight: 212.23
Distribution coefficient: 1.04 (chloroform/aqueous medium, pH 7.04, room temperature)
Description: Zonisamide is a white to pale yellow crystal or crystalline powder. It is soluble in acetone, sparingly soluble in methanol, and very slightly soluble in ethanol (95).

■Usage Precautions
○Storage: At room temperature
○Refer to the expiration date specified on the package.

■Packaging
CONSAVE Tablet 25 mg: 100 tablets (10 tablets × 10)
CONSAVE Tablet 100 mg: 60 tablets (10 tablets × 6)

Manufactured and Distributed by
Sumitomo Pharma Animal Health Co., Ltd.
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