Sprinkazen (100mg & 200mg)

Topiramate 100mg & 200 mg

Company Name: Medizen Pharmaceutical Industries.

Pharmaceutical Form:

Film-coated tablets.

Composition:

Each film-coated tablet contains:

Active Ingredients:

Topiramate 100 - 200 mg.

Inactive Ingredients:

Starch, lactose, talc, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, HPMC and titanium dioxide.

Clinical Pharmacology:

Mechanism of Action: The precise mechanisms by which topiramate exerts its anticonvulsant and migraine prophylaxis effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

Pharmacokinetics:

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours. The bioavailability of topiramate is not affected by food. The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15-41% bound to human plasma proteins over the blood concentration range of 0.5-250 µg/mL. The fraction bound decreased as blood concentration increased.

Metabolism and Excretion: Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose.) Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis and glucuronidation. There is evidence of renal tubular reabsorption of topiramate

Indications and Usage:

Monotherapy Epilepsy: Sprinkazen is indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures.

Adjunctive Therapy Epilepsy: Sprinkazen is indicated as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Migraine: Sprinkazen is indicated for adults for the prophylaxis of migraine headache.

Dosage and Administration:

Epilepsy:

Sprinkazen can be taken irrelevant to meals.

Monotherapy Use: The recommended dose for topiramate monotherapy in adults and children 10 years of age and older is 400 mg/day in two divided doses. The dose should be achieved by titrating according to the following table:

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

Adjunctive Therapy Use: ***Adults (17 Years of Age and Over) - Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome*:** The recommended total daily dose of Sprinkazen as adjunctive therapy in adults with partial seizures is 200-400 mg/day in two divided

doses and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. It is recommended that therapy be initiated at 25-50 mg/day followed by titration to an effective dose in increments of 25-50 mg/week. ***Pediatric Patients (Ages 2-16 Years) - Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome*:** The recommended total daily dose of Sprinkazen (topiramate) as adjunctive therapy is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses) to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

Migraine: The recommended total daily dose of Sprinkazen in prophylaxis of migraine headache is 100 mg/day administered in two divided doses. The recommended titration rate for topiramate for migraine prophylaxis to 100 mg/day is:

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.

Patients with Renal Impairment: In renal-impaired subjects (creatinine clearance less than 70 mL/min/1.73m^2), one half of the usual adult dose is recommended.

Patients Undergoing Hemodialysis: Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. The actual adjustment should take into account 1- the duration of dialysis period, 2- the clearance rate of the dialysis system being used, and 3- the effective renal clearance of topiramate in the patient being dialyzed.

Contraindications:

Sprinkazen is contraindicated in patients with a history of hypersensitivity to any component of this product.

Warnings:

1-Metabolic Acidosis: Hyperchloremic, 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 topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet or drugs) may be additive to the bicarbonate lowering effects of topiramate. Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered. **2- Acute Myopia and Secondary Angle Closure Glaucoma**

3-Oligohidrosis (decreased sweating) **and Hyperthermia:** Caution should be used when Sprinkazen if prescribed with other drugs that predispose patients to heat-related disorders. These drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

4-Withdrawal of AEDs: In patients with or without a history of seizures or epilepsy, antiepileptic drugs including Sprinkazen, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency.

Precautions:

Hyperammonemia and Encephalopathy Associated with Concomitant Valproic Acid Use: Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in the level of consciousness and/or cognitive functions with lethargy or vomiting and ammonia levels should be measured. **Kidney Stones**: Carbonic anhydrase inhibitors e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of **Sprinkazen** with other carbonic anhydrase inhibitors or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation and should therefore be avoided. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation. **Paresthesia** (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors.

Adjustment of Dose in Renal Failure: The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required in patients with reduced renal functions.

Decreased Hepatic Functions: In hepatic-impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Drug Interactions:

CNS Depressants: Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants. **Oral Contraceptives:** The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with Sprinkazen. **Hydrochlorothiazide (HCTZ):** The results indicate that topiramate C_{max} increased by 27% when HCTZ was added to topiramate. **Metformin:** When Sprinkazen is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state. **Pioglitazone:** When Sprinkazen is added to pioglitazone therapy or pioglitazone is added to Sprinkazen therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state. **Risperidone:** Patients receiving risperidone in combination with topiramate should be closely monitored for clinical response.

Pregnancy & Lactation:

There are no studies using Sprinkazen in pregnant women. Sprinkazen should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. The excretion of topiramate in human milk has not been evaluated in controlled studies. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to Sprinkazen is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing.

Adverse Reactions:

Weight decrease, upper respiratory tract infections, paresthesia, anorexia, diarrhea, somnolence, psychomotor slowing, dizziness, nausea, ataxia, speech disorders, abnormal vision, difficulty with memory, diplopia, fatigue, nervousness, difficulty with concentration or attention, confusion, depression, language problems, anxiety, mood problems, vasodilation, syncope, hypotension, postural hypotension, angina pectoris, tongue paralysis, hemorrhoids, stomatitis, melena, gastritis, esophagitis, urticaria, photosensitivity reaction, abnormal hair texture, urinary retention, face edema, renal pain, albuminuria, polyuria, oliguria, flushing, deep vein thrombosis, phlebitis and vasospasm.

Vision Disorders: Frequent: conjunctivitis, abnormal accommodation, photophobia and strabismus. Rare: mydriasis and iritis.

Package:

Sprinkazen 100 mg: Carton box containing 3 pvdc/aluminum strips; each strip has 10 film-coated tablets with the insert leaflet.

Sprinkazen 200 mg: Carton box containing 3 pvdc/aluminum strips; each strip has 10 film-coated tablets with the insert leaflet.

Storage:

Keep out of reach of children.

Keep at a temperature not exceeding 30°C in a dry place.

Instructions for Patients:

-Keep this leaflet. You may need to read it again.

-If you have any further questions, ask your doctor or pharmacist.

-This medicine has been prescribed for you. Do not pass it on to others; it may harm them even if their symptoms are the same as yours.

-If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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