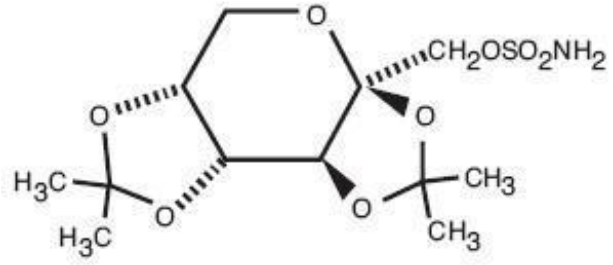
TOPIRAMATE- topiramate tablet
Bryant Ranch Prepack

Topiramate Tablets Rx Only

DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide. Topiramate Tablets are available as 25 mg, 50 mg, 100 mg, and 200 mg round tablets for oral administration.

Topiramate USP is a white crystalline powder with a bitter taste. Topiramate USP is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate USP has the molecular formula C12H21NO8S and a molecular weight of 339.37. Topiramate USP is designated chemically as 2,3:4,5-Di- -isopropylidene-β-Dfructopyranose sulfamate and has the following structural formula: *O*



Topiramate tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pre-gelatinized starch, lactose monohydrate, sodium starch glycolate, magnesium stearate, opadry white (titanium dioxide, hypromellose 3cp, hypromellose 6cp, PEG 400, polysorbate 80) for 25 mg tablets, opadry yellow (titanium dioxide, hypromellose 3cp, hypromellose 6cp, PEG 400, polysorbate 80, iron oxide yellow) for 50 mg tablets, opadry yellow (hypromellose 3cp, hypromellose 6cp titanium dioxide, PEG 400, iron oxide yellow, polysorbate 80, iron oxide red) for 100 mg tablets and), opadry pink (titanium dioxide, hypromellose 6cp, PEG 400, iron oxide red) for 200 mg tablets.

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanisms by which topiramate exerts its anticonvulsant effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy. 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.

Pharmacodynamics

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the GABA receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures

induced in rats by kindling of the amygdala or by global ischemia. A

Pharmacokinetics

The sprinkle formulation is bioequivalent to the immediate release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). 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% to 41% bound to human plasma proteins over the blood concentration range of 0.5 to 250 mcg/mL. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 mcg/mL (a concentration 5 to 10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

CLINICAL STUDIES

The studies described in the following sections were conducted using topiramate tablets.

INDICATIONS AND USAGE

CONTRAINDICATIONS

Topiramate tablets are contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS

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. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period.Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild moderate(average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. 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.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of persistent treatment-emergent decreases in serum bicarbonate in adults in the epilepsy controlled clinical trial for monotherapy was 15% for 50 mg/day and 25% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in the adjunctive therapy trials was 3% for 400mg/day, and 0% for placebo and in the monotherapy trial was 1% for 50 mg/day and 7% for 400

mg/day. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (<16 years of age), the incidence of persistent treatment emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was 67% for topiramate (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for topiramate and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

In pediatric patients (10 years up to 16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in the epilepsy controlled clinical trial for monotherapy was 7% for 50 mg/day and 20% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17mEq/L and >5 mEq/L decrease from pretreatment) in this trial was 4% for 50mg/day and 4% for 400 mg/day.

The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and <1% for placebo.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosisin pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

PRECAUTIONS

Laboratory Tests

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended (see). WARNINGS

Drug Interactions

studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 isozymes. *In vitro*

Drug/Laboratory Test Interactions

There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75 and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady-state exposures measured in patients receiving

topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady-state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a mg/m basis). [2]

Topiramate did not demonstrate genotoxic potential when tested in a battery of and assays. Topiramate was not mutagenic in the Ames test or the mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes ; and it did not increase chromosomal aberrations in human lymphocytes or in rat bone marrow . *in vitroin vivoin vitroin vitroin vitroin vivo*

No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m basis). [2]

Pregnancy: Pregnancy Category C.

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose(RHD=400 mg/day) on a mg/m2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30 and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHDon a mg/m2 basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on amg/m2 basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg orgreater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times theRHD on a mg/m2 basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on amg/m2 basis).

Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times theRHD on a mg/m2 basis) and reductions in pre- and/or post weaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m2 basis) and above. Maternaltoxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg orgreater.

In a rat embryo/fetal development study with a post natal component (0.2, 2.5, 30or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m2 basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m2 basis) and higher.

There are no studies using Topiramate in pregnant women. Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. *in utero*

Labor and Delivery

In studies of rats where dams were allowed to deliver pups naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day.

The effect of topiramate on labor and delivery in humans is unknown.

Nursing Mothers

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive secretion of topiramate into breast milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to topiramate is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing.

Pediatric Use

Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures or seizures associated with Lennox-Gastaut Syndrome. Safety and effectiveness in patients below the age of 10 years have not been established for the monotherapy treatment of epilepsy. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia/rickets and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated (see). WARNINGS

Geriatric Use

In clinical trials, 3% of patients were over 60. No age related difference in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate ≤70 mL/min/1.73 m) due to reduced clearance of topiramate (see and). ^{2}CLINICAL PHARMACOLOGYDOSAGE AND ADMINISTRATION

ADVERSE REACTIONS

The data described in the following section were obtained using topiramate tablets.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of topiramate has not been evaluated in human studies.

OVERDOSAGE

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving topiramate.

Topiramate overdose has resulted in severe metabolic acidosis (see). WARNINGS

A patient who ingested a dose between 96 g and 110 g topiramate was admitted to hospital with coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

In acute topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate . Treatment

should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body. *in vitro*

DOSAGE AND ADMINISTRATION

Topiramate 50mg Tablet

TOPIRAMATE

topiramate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63629-3995(NDC:31722-279)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TOPIRAMATE (UNII: 0H73WJJ391) (TOPIRAMATE - UNII:0H73WJJ391)	TOPIRAMATE	50 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	

POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	

Product Characteristics			
Color	YELLOW	**Score**	no score
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	IG;279
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-3995-1	30 in 1 BOTTLE		
2	NDC:63629-3995-2	60 in 1 BOTTLE		
3	NDC:63629-3995-3	90 in 1 BOTTLE		
4	NDC:63629-3995-4	120 in 1 BOTTLE		
5	NDC:63629-3995-5	7 in 1 BOTTLE		
6	NDC:63629-3995-6	80 in 1 BOTTLE		
7	NDC:63629-3995-7	14 in 1 BOTTLE		
8	NDC:63629-3995-8	45 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079162	03/27/2009	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-3995) , RELABEL(63629-3995)