Topirate® Benta

Topiramate

FORMS AND PRESENTATION

Topirate® 25 Benta: Film coated tablets: Box of 60.
Topirate® 50 Benta: Film coated tablets: Box of 60.
Topirate® 100 Benta: Film coated tablets: Box of 60.
Topirate® 200 Benta: Film coated tablets: Box of 60.

COMPOSITION:

Topirate® 25 Benta: Each film coated tablet contains Topiramate 25mg.
Excipients: Lactose, starch, croscarmellose sodium, povidone, colloidal silicon dioxide 200, crospovidone, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide, glyceryl monocaprylocaprate, sodium lauryl sulfate, yellow iron oxide, red iron oxide.
Topirate® 50 Benta: Each film coated tablet contains Topiramate 50mg.
Topirate® 100 Benta: Each film coated tablet contains Topiramate 100mg.
Excipients: Lactose, microcrystalline cellulose, starch, croscarmellose Sodium, povidone, sodium starch glycolate, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide, glyceryl monocaprylocaprate, sodium lauryl sulfate, yellow iron oxide, FD&C yellow#5 , FD&C blue#2.
Topirate® 200 Benta: Each film coated tablet contains Topiramate 200mg.
Excipients: Lactose, microcrystalline cellulose, starch, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate, red iron oxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Therapeutic class: Antiepileptics.
ATC code: N03AX11.
Topiramate is classified as a sulfamate-substituted monosaccharide. The precise mechanism by which Topiramate exerts its antiseizure and migraine prophylaxis effects is unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of Topiramate.
Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by Topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which γ-aminobutyrate (GABA) activated $GABA_A$ receptors, and enhanced the ability of GABA to induce a flux of chloride ions into neurons, suggesting that Topiramate potentiates the activity of this inhibitory neurotransmitter.
This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did Topiramate increase the duration of the channel open time, differentiating Topiramate from barbiturates that modulate $GABA_A$ receptors.
Because the antiepileptic profile of Topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor. Topiramate antagonized the ability of kainate to activate the kainate/AMPA (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid)
subtype of excitatory amino acid (glutamate) receptor, but had no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of Topiramate were concentration-dependent over a range of 1 µM to 200 µM, with the
minimum activity observed at 1µM to 10µM.
In addition, Topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of Topiramate's antiepileptic activity.
In animal studies, Topiramate exhibits anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests and is 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. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole.
Studies in mice receiving concomitant administration of Topiramate and carbamazepine or phenobarbital showed synergistic anticonvulsant activity, while combination with phenytoin showed additive anticonvulsant activity. In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of Topiramate and its clinical efficacy. No evidence of tolerance has been demonstrated in man.

Pharmacokinetic Properties

The pharmacokinetic profile of Topiramate compared to other antiepileptic drugs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites.
Topiramate is not a potent inducer of drug metabolizing enzyme, can be administered without regard to meals, and routine monitoring of plasma Topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.
Absorption: Topiramate is rapidly and well absorbed. Following oral administration of 100 mg Topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of 1.5 µg/ml was achieved within 2 to 3 hours (T_{max}). Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of ^{14}C-Topiramate was at least 81%. There was no clinically significant effect of food on the bioavailability of Topiramate.
Distribution: Generally, 13 to 17% of Topiramate is bound to plasma protein. A low capacity binding site for Topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/ml has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 l/kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.
Metabolism: Topiramate is not extensively metabolized (~20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and faeces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of ^{14}C-Topiramate. Two metabolites, which retained most of the structure of Topiramate, were tested and found to have little or no anticonvulsant activity.
Elimination: In humans, the major route of elimination of unchanged Topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of ^{14}C-Topiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of Topiramate the mean renal clearance was approximately 18 ml/min and 17 ml/min, respectively. There is evidence of renal tubular reabsorption of Topiramate. Overall, plasma clearance is approximately 20 to 30 ml/min in humans following oral administration.
Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. The pharmacokinetics of Topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 100 to 400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. The mean C_{max} following multiple, twice a day oral doses of 100 mg to healthy subjects was 6.76 µg/ml. Following administration of multiple doses of 50 mg and 100 mg of Topiramate twice a day, the mean plasma elimination half-life was approximately 21 hours.
Concomitant multiple-dose administration of Topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of Topiramate.
The plasma and renal clearance of Topiramate are decreased in patients with impaired renal function (CL_{CR} ≤60 ml/min), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state Topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. Topiramate is effectively removed from plasma by hemodialysis.
Plasma clearance of Topiramate is decreased in patients with moderate to severe hepatic impairment.
Plasma clearance of Topiramate is unchanged in elderly subjects in the absence of underlying renal disease.
Pediatric population (pharmacokinetics, up to 12 years of age)
The pharmacokinetics of Topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of Topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing antiepileptic drugs decrease the steady-state plasma concentrations.

INDICATIONS

- Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalized seizures, and primary generalized tonic-clonic seizures.
- Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.
- Topirate® Benta is indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topirate® Benta is not intended for acute treatment.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Migraine prophylaxis in pregnancy and in women of childbearing potential if not using effective methods of contraception.

PRECAUTIONS

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency or the onset of new types of seizures with Topiramate. These phenomena may be the consequence of an overdose, a decrease in plasma concentrations of concomitantly used antiepileptics, progress of the disease or a paradoxical effect.
Mood disturbances/depression: An increased incidence of mood disturbances and depression has been observed during Topiramate treatment.
Suicide/suicidal ideation: Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Topiramate.
Therefore patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Nephrolithiasis: Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Adequate hydration while using Topiramate can reduce the risk of nephrolithiasis.
Acute myopia and secondary angle closure glaucoma: Symptoms include acute onset of decreased visual acuity and/or ocular pain. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with Topiramate has been reported in paediatric patients as well as adults. Treatment includes discontinuation of Topiramate and appropriate measures to reduce intraocular pressure.
Metabolic acidosis: Hyperchloremic, non-anion gap, metabolic acidosis is associated with Topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of Topiramate on renal carbonic anhydrase. Chronic metabolic acidosis increases the risk of renal stone formation and may potentially lead to osteopenia. Chronic metabolic acidosis in pediatric patients can reduce growth rates.
Nutritional supplementation
A dietary supplement or increased food intake may be considered if the patient is losing weight while on Topiramate.
Lactose intolerance
This drug contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

Ability to drive and use machines

Topiramate acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms. It may also cause visual disturbances and/or blurred vision. These adverse reactions could potentially be dangerous in patients driving a vehicle or operating machinery.

PREGNANCY AND LACTATION

Pregnancy registry data suggest that there may be an association between the use of Topiramate during pregnancy and congenital malformations. This has been reported with Topiramate monotherapy and Topiramate as part of a polytherapy regimen (there may be an increased risk of teratogenic effects associated with the use of antiepileptic drugs in combination therapy).
It is recommended that women of child bearing potential use adequate contraception.
Limited observations in patients suggest an extensive excretion of Topiramate into breast milk. A decision must be made whether to suspend breast-feeding or to discontinue Topiramate therapy.

DRUG INTERACTIONS

Effects of Topiramate on other antiepileptic medicinal products
The addition of Topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state

plasma concentrations, except in the occasional where the addition of Topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

Effects of other antiepileptic medicinal products on Topiramate

Phenytoin and carbamazepine decrease the plasma concentration of Topiramate. The addition or withdrawal of valproic acid or lamotrigine does not produce clinically significant changes in plasma concentrations of Topiramate. Phenobarbital's and primidone's effects on Topiramate concentration are not studied.

Other medicinal product interactions

Digoxin

In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of Topiramate.

CNS depressants

It is recommended that Topiramate not be used concomitantly with alcohol or other CNS depressant medicinal products.

St John's Wort (Hypericum perforatum)

A risk of decreased plasma concentrations resulting in a loss of efficacy could be observed with co-administration of Topiramate and St John's Wort.

Oral contraceptives

The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with Topiramate. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

Lithium

Lithium levels should be monitored when co-administered with Topiramate.

Risperidone

When administered concomitantly with Topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone systemic exposure. However, differences in AUC for the total active moiety between treatment with risperidone alone and combination treatment with Topiramate were not statistically significant. When Topiramate was added to existing risperidone (1-6 mg/day) treatment, adverse events were reported more frequently than prior to Topiramate (250-400 mg/day) introduction (90% and 54 % respectively).

Hydrochlorothiazide (HCTZ)

The addition of HCTZ to Topiramate therapy may require an adjustment of the Topiramate dose since the C_{max} and the AUC of this latest one increased when HCTZ was added to Topiramate. Clinical laboratory results indicated decreases in serum potassium after Topiramate or HCTZ administration, which were greater when HCTZ and Topiramate were administered in combination.

Metformin

The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When Topiramate 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, Glyburide

When Topiramate is added to pioglitazone or glyburide therapy or, pioglitazone or glyburide are added to Topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Other forms of interactions

Agents predisposing to nephrolithiasis

While using Topiramate, agents predisposing to nephrolithiasis should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Valproic acid

Concomitant administration of Topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone.

ADVERSE EFFECTS

The safety of Topiramate was evaluated from a clinical trial database for Topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The most common ADRs identified in double blind controlled studies include: anorexia, decreased appetite, bradyphrenia, depression, expressive language disorder, insomnia, coordination abnormal, disturbance in attention, dizziness, dysarthria, dysgeusia, hypoesthesia, lethargy, memory impairment, nystagmus, paresthesia, somnolence, tremor, diplopia, blurred vision, diarrhea, nausea, fatigue, irritability, and weight decrease.

Pediatric population

ADRs reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, hyperchloremic acidosis, hypokalemia, abnormal behavior, aggression, apathy, initial insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, increased lacrimation, sinus bradycardia, feeling abnormal and gait disturbance. ADRs that were reported in children but not in adults in double-blind controlled studies include: eosinophilia, psychomotor hyperactivity, vertigo, vomiting, hyperthermia, pyrexia and learning disability.

DOSAGE AND ADMINISTRATION

General

It is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Dose and titration rate should be guided by clinical response. Topirate® Benta is available in film coated tablets. It is recommended that film coated tablets not be broken. It is not necessary to monitor Topiramate plasma concentrations to optimize therapy with Topirate® Benta. On rare occasions, the addition of Topirate® Benta to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and carbamazepine to adjunctive therapy with Topirate® Benta may require adjustment of the dose of Topirate® Benta.

Topirate® Benta can be taken without regard to meals.

In patients with or without a history of seizures or epilepsy, antiepileptic drugs including Topirate® Benta should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving doses up to 100 mg/day for migraine prophylaxis. In paediatric clinical trials, Topiramate was gradually withdrawn over a 2-8 week period.

Monotherapy epilepsy

General

When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with Topirate® Benta, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AED, a gradual discontinuation at the rate of approximately one-third of the concomitant AED dose every 2 weeks is recommended.

When enzyme inducing medicinal products are withdrawn, Topirate® Benta levels increase. A decrease in Topirate® Benta dosage may be required if clinically indicated.

Adults

Dose and titration should be guided by clinical response. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1 or 2 week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used.

The recommended initial target dose for Topirate® Benta monotherapy in adults is 100 mg/day to 200 mg/day in 2 divided doses. The maximum recommended daily dose is 500 mg/day in 2 divided doses. Some patients with refractory forms of epilepsy have tolerated Topirate® Benta monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

Pediatric population (children over 6 years of age)

Dose and titration rate in children should be guided by clinical outcome. Treatment of children over 6 years of age should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1 or 2 week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. The recommended initial target dose range for Topirate® Benta monotherapy in children over 6 years of age is 100 mg/day depending on clinical response (this is about 2 mg/kg/day in children 6-16 years).

Adjunctive therapy epilepsy (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome)

Adults

Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials as adjunctive therapy, 200 mg was the lowest effective dose. The usual daily dose is 200-400 mg in two divided doses.

Pediatric population (children aged 2 years and above)

The recommended total daily dose of Topirate® Benta 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. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Migraine

Adults

The recommended total daily dose of Topirate® Benta for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.

Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. This dose may be of benefit in some patients, nevertheless, caution is advised due to an increased incidence of side effects.

Pediatric population

Topirate® Benta is not recommended for treatment or prevention of migraine in children due to insufficient data on safety and efficacy.

General dosing recommendations for Topirate® Benta in special patient populations

Renal impairment

In patients with impaired renal function, Topirate® Benta should be administered with caution as the plasma and renal clearance of Topiramate are decreased. Subjects with known renal impairment may require a longer time to reach steady-state at each dose.

In patients with end-stage renal failure, since Topiramate is removed from plasma by hemodialysis, a supplemental dose of Topirate® Benta equal to approximately one-half the daily dose should be administered on hemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the hemodialysis procedure.

Hepatic impairment

In patients with moderate to severe hepatic impairment Topirate® Benta should be administered with caution as the clearance of Topiramate is decreased.

Elderly

No dose adjustment is required in the elderly population providing renal function is intact.

OVERDOSAGE

Signs and symptoms

Overdoses of Topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, 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 overdoses with multiple medicinal products including Topiramate.

Topiramate overdose can result in severe metabolic acidosis.

Treatment

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 *in vitro*. Treatment should be appropriately supportive and the patient should be well hydrated. Hemodialysis has been shown to be an effective means of removing Topiramate from the body.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: November 2017.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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