CTD MODULE 2

2.5. CLINICAL OVERVIEW

TOPIRAMATE ROSEMONT 10 MG/ML AND 20 MG/ML ORAL SUSPENSION

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ABBREVIATIONS

AE	Adverse Event
AED	Antiepileptic Drug
ANOVA	Analysis Of Variance
AUC	Area Under the plasma concentration-time Curve
BMI	Body Mass Index
CI	Confidence Interval
CL/F	oral plasma Clearance
CL_{CR}	Creatinine Clearance
CLR	Renal Clearance
C_{max}	maximum (peak) plasma/serum Concentration
CNS	Central Nervous System
CV	Coefficient of Variation
ECG	Electrocardiogram
EEG	Electroencephalogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCTZ	Hydrochlorothiazide
MES	Maximal Electroshock Seizure
NMDA	N-Methyl-D Aspartate
NNH	Number Needed to Harm
NNT	Number Needed to Treat
OR	Odds Ratio
PI	Protective Index
SD	Standard Deviation
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
$t_{1/2\beta}$	terminal elimination half-life
TD_{50}	Toxic Dose (50% kill)
t_{max}	time to the maximum plasma/serum concentration
V	apparent Volume of distribution

2.5.1. Product Development Rationale

The primary therapeutic approach in treating epilepsy is oral administration of antiepileptic drugs, which prevent seizures by raising seizure threshold or by blocking their spread. Current antiepileptic drugs fail to control seizures adequately in as much as 30% of patient population and are associated with adverse events. Therefore, the discovery of highly effective and well-tolerated antiepileptic drugs continues to be a major objective in medical research.

Topiramate is structurally distinct from other known antiepileptic drugs in that it is a derivative of the naturally occurring monosaccharide D-fructose and contains a sulfamate functionality. Topiramate was selected for development as an antiepileptic drug based on its potency, high protective index, and long duration of action.

In vivo and *in vitro* preclinical studies indicate that topiramate has multiple mechanisms of action (blockade of voltage-dependent Na^+ channels; potentiation of gamma-aminobutyric acid (GABA); antagonism of a kainate subtype of the glutamate receptor, and inhibition of carbonic anhydrase) and suggest a broad spectrum of anticonvulsant activity. In humans, topiramate exhibits a favourable pharmacokinetic profile, including rapid absorption, long duration of action, and minimal interaction with other antiepileptic drugs.

Topiramate is indicated as monotherapy in adults and children aged 6 years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures. Topiramate is indicated as adjunctive therapy for adults and children over 2 years of age who are inadequately controlled on conventional first line antiepileptic drugs for: partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut syndrome and primary generalised tonic-clonic seizures. Topiramate is also indicated in adults for the prophylaxis of migraine headache.

In humans, adverse effects associated with topiramate therapy include ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia or hypoaesthesia, drowsiness, and difficulties with memory or cognition. Agitation, anxiety, nervousness, emotional lability (with mood disorders), and depression may also occur. Other reported adverse effects include abdominal pain, anorexia, asthenia, diplopia, leucopenia, nausea, nystagmus, insomnia, psychomotor retardation, impaired speech, altered taste, visual disturbances, and weight loss. The risk of developing renal calculi is increased, especially in predisposed patients. Reduced sweating with hyperthermia has occurred particularly in children. Rare cases of acute myopia with secondary angle-closure glaucoma have been reported.

This Clinical Overview is based entirely on published scientific literature. Searches were carried out in bibliographic databases. Specific search criteria were used, adjusted to the specific database terminology, scope and structure, covering all aspects required for this overview. Primarily English language literature was selected initially on the basis of search results including abstracts, and subsequently on the basis of original publications acquired. Where necessary, reference lists of original publications were searched manually for complementary publications. The available data from FDA and EMA website were also included.

This overview has been prepared as part of a marketing authorisation application to market a formulation of Topiramate Rosemont 10 mg/ml and 20 mg/ml Oral Suspension.

2.5.2. Overview of Biopharmaceutics

An open label, balanced, randomized, three-treatment, three-period, three-sequence, single oral dose, crossover, comparative bioavailability study of Topiramate Suspension 20 mg/mL (test-1) and Topiramate Suspension 10 mg/mL (test-2) with reference to Topamax® 200 mg film coated Tablets (reference) in normal, healthy, adult, human male subjects under fasting condition

The aim of this study was to compare the rate and extent of absorption of the sponsor's two test products relative to that of reference product after single oral dose administration in normal, healthy, adult, human male subjects under fasting condition and to characterize the pharmacokinetic profile. The safety and tolerability of a single dose of topiramate in healthy adult human male subjects under fasting conditions were also monitored.

The study was been conducted as per the protocol, GCP and based on the applicable principles of Good Laboratory Practice (GLP) and SOPs of Lambda Therapeutic Research Ltd., at Lambda Therapeutic Research Limited, Lambda House House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382481, Gujarat, India between 25 April 2017 and 20 May 2017.

The study was an open label, balanced, randomized, three-sequence, three-treatment, three-period, single oral dose, crossover, comparative bioavailability study in normal, healthy, adult, human male subjects under fasting condition, with a screening period of 28 days prior to dose administration in Period-I. In each study period, 24 blood samples, including one pre-dose blood sample were collected from each subject except for the discontinued/ withdrawn subjects and missing samples to analyze the pharmacokinetic profile of the test products as well as the reference product.

Inclusion criteria were: non smokers, normal, healthy, adult, human male volunteers between 18 to 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 to 29.9 kg/m^2 (both inclusive), were able to understand and comply with the study procedures and having given their written informed consent were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray (postero-anterior view) recordings. Volunteers who complied with all the inclusion and exclusion criteria were checked in for the study.

Thirty six (36) subjects were included, 3 subjects ([redacted] were withdrawn post-dose. Subject [redacted] discontinued from the study on their own accord in Period-II. Subject [redacted] was withdrawn from the study on medical grounds in Period-III. In all, 33 subjects (Subject [redacted]) completed the clinical phase of the study successfully.

After an overnight fast of at least 10 hours, a single oral dose (10 mL) of the test product (T1: Topiramate Suspension 20 mg/mL Manufactured by: Rosemont Pharmaceuticals Ltd., Braithwaite Street, Leeds, West Yorkshire, LS11 9XE, UK.) or a single oral dose (20 mL) of the test product (T2) or a single oral dose (200 mg) of the reference product (R: Topamax® 200 mg film coated Tablets;

Marketing Authorisation Holder: Janssen Cilag Ltd. 50100, Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK) was administered with 240 mL of drinking water at ambient temperature with the subjects in sitting posture. The IMP administration was as per the randomization schedule and under open-label condition. The suspension of test products (T1 and T2) was prepared at the time of dispensing as specified on the label of study drugs or as per the recommendation by manufacturer. The tablet was swallowed whole without chewing or crushing.

For efficacy evaluation, a total of 24 blood samples were collected in each period at the time points specified in the protocol. Standard non-compartmental model of Phoenix® WinNonlin® Version 6.4 (Certara L.P.) was used to derive pharmacokinetic parameters for topiramate. Safety was assessed from the screening period to the end of the study. It was assessed through clinical examinations, vital signs assessment, 12-lead ECG, chest X-ray (postero-anterior view) recording, clinical laboratory parameters (e.g. haematology, biochemistry, urine analysis and immunology), subjective symptomatology and monitoring of adverse events.

Descriptive statistics are calculated and reported for all pharmacokinetic parameters of topiramate. ANOVA, power and ratio analysis for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are calculated and reported for topiramate. Using two-one sided tests, 90% confidence intervals for the ratio of the geometric least-squares means between drug formulations are calculated for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for topiramate. Bioavailability of the two test products with that of the reference product is concluded as comparable, if the 90% confidence interval falls within the acceptance range (80,0-125,0%) for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for topiramate.

The pharmacokinetic parameters were calculated from the plasma concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Version 6.4 (Certara L.P.) for topiramate. Statistical comparison of the pharmacokinetic parameters of the three formulations (two tests and one reference formulations) was carried out using PROC MIXED of SAS® Version 9.3 (SAS Institute Inc., USA) to assess the bioavailability between two test and one reference formulations.

The pharmacokinetic parameters of topiramate for Test Product-T1, Test Product-T2 and Reference Product-R are shown in Fig 1 and Fig 2, and summarized in Table 1.

The relative bioavailability analyses (i.e. geometric least squares means, ratio, 90% confidence interval, intra subject CV and power) of Test Product-T1 vs. Reference Product-R and Test Product-T2 vs. Reference Product-R for topiramate are summarized in Table 2.

Figure 1. Mean plasma concentration vs. time curve for Topiramate (Linear Plot)

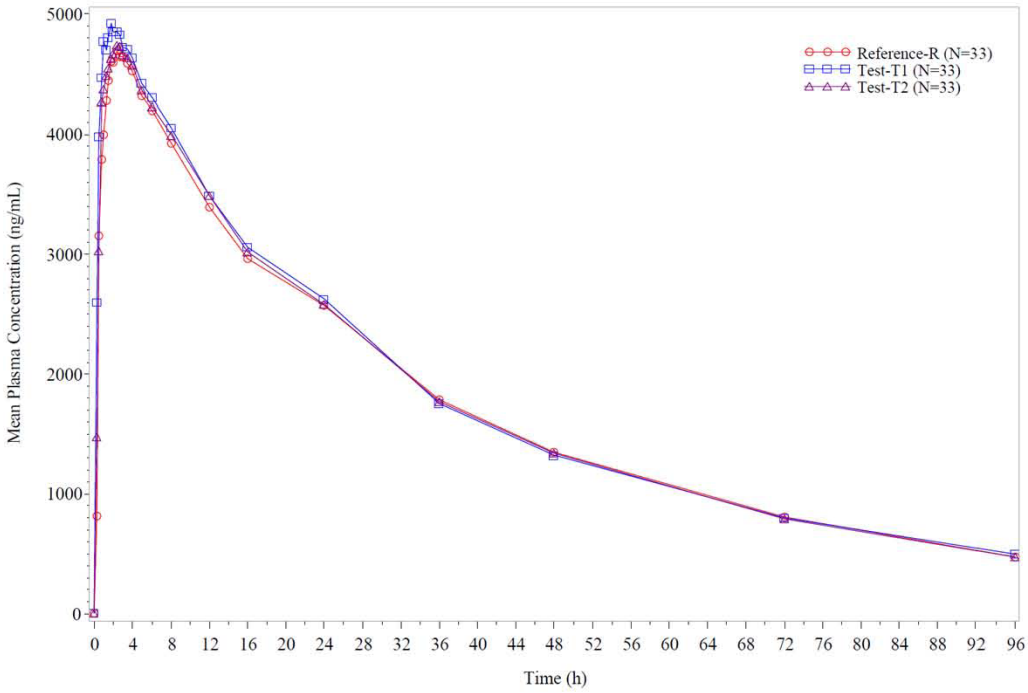

Figure 2. Mean plasma concentration vs. time curve for Topiramate (Semilog Plot)

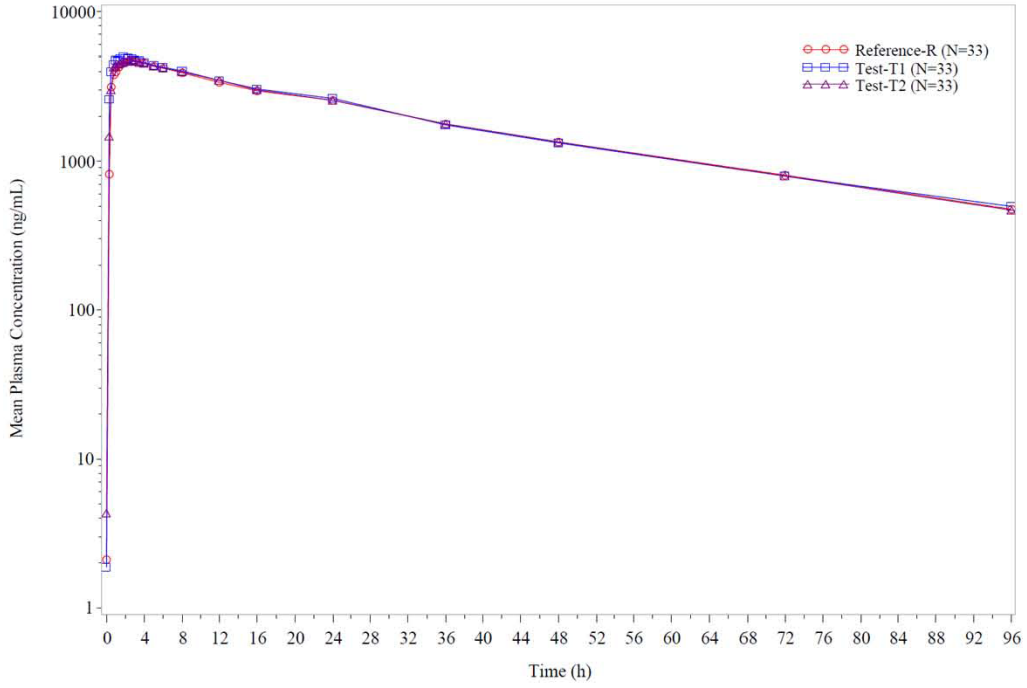

Table 1. Descriptive statistics of formulation means for topiramate (N = 33)

Parameters (Units)	Mean ± SD (untransformed data)		
	Test Product-T1	Test Product-T2	Reference Product-R
T_{max} (h)#	1.000 (0.250 - 4.000)	2.000 (0.250 - 6.000)	1.250 (0.500 - 5.000)
C_{max} (ng/mL)	5404.973 ± 1056.4541	5200.646 ± 896.7466	5296.107 ± 944.4653
AUC_{0-t} (ng.h/mL)	171754.951 ± 21994.3752	169318.859 ± 19769.7500	168036.772 ± 23285.3160
$AUC_{0-\infty}$ (ng.h/mL)	197954.544 ± 36535.3360	192365.674 ± 26540.5576	191786.954 ± 32865.0706
λ_z (1/h)	0.022 ± 0.0049	0.022 ± 0.0036	0.023 ± 0.0044
$t_{½}$ (h)	33.489 ± 10.6752	31.689 ± 5.5096	31.279 ± 6.0443
AUC_%Extrap_obs (%)	12.335 ± 6.3858	11.646 ± 4.2936	11.793 ± 5.1972

#T_{max} is represented in median (min-max) value.

Table 2. Relative bioavailability results for topiramate (N = 33)

T1 vs. R						
Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T1	Reference Product-R	Ratio (T1/R) %			
lnC_{max}	5301.159	5227.795	101.4	97.89 - 105.04	8.6	100.0
$lnAUC_{0-t}$	170456.955	167111.235	102.0	100.36 - 103.67	3.9	100.0
$lnAUC_{0-\infty}$	195207.131	190071.524	102.7	100.39 - 105.07	5.5	100.0
T2 vs. R						
Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T2	Reference Product-R	Ratio (T2/R) %			
lnC_{max}	5122.696	5227.795	98.0	94.60 - 101.51	8.6	100.0
$lnAUC_{0-t}$	168187.056	167111.235	100.6	99.03 - 102.29	3.9	100.0
$lnAUC_{0-\infty}$	190780.870	190071.524	100.4	98.11 - 102.69	5.5	100.0

Safety results:

Adverse events: Ten (10) adverse events (AEs) were reported by eight (08) subjects during the conduct of the study. Six (06) AEs were reported in Period-I, two (02) AEs were reported in Period-III and two (02) AEs were reported during post-study safety assessment of the study. Five (05) AEs were reported in the subjects after administration of Reference Product-R, one (01) AE was reported in the subject after administration of Test Product-T1 and four (04) AEs were reported in the subjects after administration of Test Product-T2. All the AEs were mild in nature. All the subjects were followed up until resolution of their AEs except for Subject [redacted] He did not report for his AE follow-up and was not traceable even after several attempts and hence he was considered to be lost to

follow-up. The causality assessment was judged as possibly related for seven (07) AEs and as unlikely related for three (03) AEs. There were no deaths or serious AEs reported during the conduct of the study. However, out of the total reported ten (10) AEs, two (02) AEs were significant. The subject was withdrawn from the study on medical grounds. He was treated appropriately and followed up until resolution of his AEs. The causality assessment was judged as unlikely related for both the AEs.

Conclusion:

The bioavailability of the Test Product-T1 and Test Product-T2 with that of the Reference Product-R is comparable with respect to C_{max} and AUC_{0-t} for topiramate under fasting condition as per criteria set in the protocol. Data from this study demonstrated that the test and the reference products were well tolerated.

2.5.3. Overview of Clinical Pharmacology

2.5.3.1. Pharmacokinetics

The clinical pharmacokinetics of topiramate has extensively been investigated, in both single-dose and multiple-dose studies in healthy volunteers and in epileptic patients receiving concomitant medication (reviewed by: *Langtry et al, 1997; Rosenfeld, 1997; Perucca & Bialer, 1996; Garnett, 2000).*

Absorption

Topiramate absorption from orally administered tablets is rapid and nearly complete, with peak plasma concentrations occurring ~2 h after a 400 mg dose. Topiramate absorption is linear across a wide range of doses, as demonstrated in a study in healthy volunteers receiving a single dose of 100-1,200 mg topiramate *(Doose et al, 1996)*. Maximal plasma concentrations (C_{max} 1.73-28.7 pg/ml) were dose proportional and were reached within 1.8-4.3 h (t_{max}).

Administration of topiramate with food affects the rate but not the extent of topiramate absorption. In a study with healthy male volunteers given a single 100 or 400 mg tablet, area under the plasma concentration-time curve (AUC) was not significantly different between topiramate administered after fasting or after a fatty breakfast; the time to C_{max} was moderately delayed (~2 h) when topiramate was administered in the fed state *(Doose et al, 1996)*. Because the extent of absorption is more important than the rate, topiramate can be administered with meals without clinically significant effects on topiramate plasma levels. In addition to the currently available tablets *(Garnett, 2000)*.

The paradigm for individualizing antiepileptic drug therapy is generally a "treatment-to-effect" approach. Antiepileptic drug dosages are usually increased incrementally to achieve the best level of seizure control with a minimum of adverse effects. This approach is most successful when titration produces a dose-proportional increase in antiepileptic drug plasma concentration. Disproportionate increases in plasma concentrations with increasing dosages introduce an element of unpredictability that makes treatment more difficult. Pharmacokinetic studies with topiramate have shown that both C_{max} and AUC were linear and increased in proportion to dose, with low intersubject variability, as the topiramate dose was increased from 200 to 800 mg. Predictable steady-state topiramate plasma concentrations were achieved regardless of dose (50, 100, or 200 mg topiramate) or dosing regimen (q.d. or bid.) *(Garnett, 2000)*.

Distribution

Topiramate appears to distribute primarily to body water. The volume of distribution of topiramate was inversely related to the dose, being 58L after a 100 mg dose, 50.8 L after a 400 mg dose and 38.5 L after a 1200 mg dose. The extent of protein binding of topiramate was 13 to 17%.

The extent of drug distribution depends, in part, on the amount of drug bound to plasma proteins. Topiramate is poorly bound to plasma proteins (9-17%). The mean apparent volume of distribution of topiramate ranged from 0.6 to 0.8 L/kg for 100-1,200 mg topiramate, consistent with distribution into total body water. Competitive protein binding may alter plasma concentrations of free drug and

increase the potential for side effects, as can medical conditions that decrease serum albumin concentrations or impair renal function. Because topiramate is poorly bound to plasma proteins, it is unlikely to displace or be displaced by highly protein-bound drugs, limiting its potential for drug interactions with highly protein-bound antiepileptic drugs as well as non-antiepileptic drugs. In addition, Topiramate plasma levels are not likely to be affected by disease states that affect plasma protein binding,

Metabolism

Topiramate is not extensively metabolized (~20%) when administered alone or in the absence of hepatic enzyme induction. In healthy male volunteers given 100 mg of radiolabeled topiramate, unchanged topiramate represented 85% of total plasma radioactivity 24 h after dosing. Six inactive metabolites formed by glucuronidation, hydroxylation, and hydrolysis have been identified. None of the metabolites constitutes >5% of an administered dose; they are quickly cleared with little or no accumulation. Hepatic enzyme induction or inhibition by coadministered drugs may have clinically significant effects on plasma concentrations of antiepileptic drugs that are metabolized in the liver. With hepatic enzyme induction, 40-50% of an administered dose of topiramate is metabolized. Topiramate clearance was increased approximately twofold in the presence of enzyme-inducing antiepileptic drugs. *In vitro* studies with human hepatic microsomes examined the potential for topiramate inhibition of seven cytochrome P-450 isozymes involved in drug metabolism (CYPIA2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). CYP2C19 was the only isozyme inhibited by topiramate.

Excretion

Topiramate is excreted primarily by the kidneys. 48 hours after administration of a single 100 mg dose of ^{14}C topiramate to 6 healthy men, ≈40% of the radioactivity in excreta was unchanged drug, and after 10 days, 80.6% of total radioactivity was recovered in the urine and 0.7% in the faeces. In healthy volunteers receiving a single 100 to 1200 mg dose of topiramate, oral clearance (CL/F) ranged from 1.4 to 2.2 L/h, renal clearance (CLR) was 0.78 to 0.88 L/h and the terminal elimination half-life ($t_{1/2\beta}$) of topiramate ranged from 19 to 25 hours. Elimination of topiramate at steady-state is similar to that after single doses. In healthy volunteers at steady-state, CL/F, CLR and $t_{1/2\beta}$ were constant across 3 dosage regimens (50 or 100 mg once daily for 14 days then twice daily for 14 days, or 200 mg once daily for 20 days), with mean values of 1.27 L/h, 0.79 L/h and 25.4 hours, respectively.

Pharmacokinetics in Special Populations

Pharmacokinetics in Patients with Renal and Hepatic Impairment

An overview of topiramate pharmacokinetics in healthy volunteers and patients with renal or hepatic impairment is given in Table 3 (after *Langtry et al, 1997).*

Predictably, moderate renal failure [creatinine clearance (CL_{CR}) 1.8 to 4.1 L/h (30 to 69 ml/min)] or severe renal failure [CL_{CR} <1.8 L/h (<30 ml/min)] resulted in a significant decrease in CLR and increase in AUC and $t_{1/2\beta}$ compared with normal renal function [CL_{CR} >4.1 L/h (>70 ml/min)]; C_{max} remained unaffected. Plasma

topiramate concentrations decreased by ≈50% during haemodialysis 32 to 35 hours after a single topiramate 100 mg dose in 6 patients with end-stage renal disease. The clearance of topiramate from plasma during haemodialysis was about 9 times taster than normal (7.41 vs. 0.79 L/h); thus, these patients would require additional doses of topiramate to maintain therapeutic drug concentrations.

Table 3. Mean pharmacokinetic values for topiramate in fasted healthy volunteers or patients with renal or hepatic impairment after a single oral dose of topiramate 100 mg (after *Langtry et al, 1997)*

Parameter	Healthy volunteers (n = 6)	Renal impairment (n = 7 each group)				Hepatic impairment[d] (n = 5)[e]
		moderate[a]	none[b]	severe[c]	none[b]	
C_{max} (mg/L)	1.73	1.9	1.6	2.1	2.2	
C_{max} (h)	1.75					
V (L)	58					
CL/F (L/h)	2.2	0.8*	1.4	0.55*	1.2	1.41
CLR (L/h)	0.79	0.37*	0.79	0.15*	0.65	
AUC (mg/L • h)	45	137*	74	88*	88	
$t_{1/2\beta}$ (h)	19	55*	38	59*	32	33.6

[a] CL_{CR} 1.8 to 4.1 L/h (30-69 ml/min).
[b] Healthy volunteers, CL_{CR} ≥4.2 L/h (>70 ml/min), matched for age, weight and gender.
[c] CL_{CR} <1.8 L/h (<30 ml/min).
[d] Defined as Child-Pugh score of 5-9.
[e] Reported as an abstract.
* indicates significance compared with paired control group (level of significance not stated).

CL/F was lower (1.41 vs. 1.91 L/h) and $t_{1/2\beta}$ was higher (33.6 vs. 24.7 hours) in 5 patients with moderate or severe stable liver impairment (Child-Pugh score 5 to 9) after a single topiramate 100 mg dose compared with values in healthy age-, weight- and gender-matched volunteers. The resultant increase in plasma drug concentration, although not reported in this abstract, was not thought by the investigators to be clinically significant.

Pharmacokinetics in Children

After 1 week of topiramate 1, 3 and 9 mg/kg/ day, linear pharmacokinetics, dose-independent clearance and dose-proportional steady-state plasma concentrations were seen in children with epilepsy (4 to 17 years) receiving 1 or 2 other antiepileptic drugs (data on file, reviewed by *Langtry et al, 1997; Rosenfeld et al, 1999)*. Enzyme-inducing antiepileptic drugs reduced the half-life of topiramate from 15.4 to 7.5 hours. Topiramate clearance is reported to be 50% higher in children than in adults, resulting in plasma topiramate concentrations that are 33% lower in children.

The pharmacokinetics of topiramate was studied in a cohort of infants (younger than 4 years) participating in an open-label trial of topiramate in refractory infantile spasms *(Glauser et al, 1999)*. The pharmacokinetics of topiramate were assessed in infants receiving a stable topiramate dose for >7 days during the extension phase of this trial. Blood samples were drawn just before and 0.5, l , 1.5, 2, 4, 6, 8, and 12 h after the morning topiramate dose. Topiramate plasma concentrations

were determined by fluorescence polarization immunoassay. The non-compartmental analysis module of WinNonlin was used to calculate individual patient pharmacokinetics profiles. Five infants (ages, 23.5-29.5 months) formed the study cohort. These infants had been given topiramate for a median of 9 months (range, 6-11 months) and were currently receiving between 11 and 38.5 mg/kg/day topiramate. One was receiving topiramate monotherapy, whereas four were taking concomitant antiepileptic medications (n = 2, enzyme-inducing agents; n= 2, non-enzyme-inducing drugs). Topiramate pharmacokinetics in infants appears to be linear. In this cohort, mean topiramate plasma clearance (CL/F, 66.6 ± 27.4 ml/h/kg) was slightly higher than that reported for children and adolescents and therefore substantially higher than that reported for adults. Topiramate CL/F was higher and the calculated half-life shorter in the infants receiving concomitant enzyme-inducing antiepileptic drugs. The authors conclude that based on this small cohort of patients, it appears that infants may require significantly larger topiramate doses, based on weight, than children, adolescents, or adults. Titration to effect and not absolute topiramate dose should guide therapy in this age group *(Glauser et al, 1999)*.

In one study the steady-state pharmacokinetics of topiramate was compared in a large population of children and adults with epilepsy in a therapeutic drug monitoring setting *(Battino et al, 2005).* Seventy children (aged 1–17 years) with epilepsy and 70 adult controls (aged 18–65 years) with epilepsy, matched for sex and comedication. Topiramate apparent oral clearance (CL/F) values were calculated from steady-state serum concentrations in children and compared with those determined in controls. Comparisons were made by means of the Mann-Whitney's U-test, or the Kruskal-Wallis test in the case of multiple comparisons. A linear regression model was used to assess potential correlation of CL/F values with age. To investigate the influence of different variables on the variability in topiramate CL/F values, a multiple regression model was developed. In the absence of enzyme-inducing comedication, mean topiramate CL/F was 42% higher in children than in adults (40.3 ± 21.0 vs. 28.4 ± 15.3 mL/h/kg; $p < 0.01$). In children and adults co-administered with enzyme-inducing antiepileptic drugs, topiramate CL/F values were approximately 1.5- to 2-fold higher than those observed in the absence of enzyme inducers, and the elevation in topiramate CL/F in children compared with adults was also present in the subgroups receiving enzyme inducers (66%; 76.6 ± 35.1 vs. 46.1 ± 16.7 mL/h/kg; $p < 0.0001$). In the paediatric population, a negative correlation between CL/F and age was demonstrated, both in the absence ($p < 0.01$) and in the presence ($p < 0.001$) of enzyme induction. The independent influence of age and enzyme-inducing antiepileptic drugs on topiramate CL/F was confirmed by multiple regression analysis. The authors conclude that topiramate CL/F is highest in young children and decreases progressively with age until puberty, presumably due to age-dependent changes in the rate of drug metabolism. As a result of this, younger patients require higher dosages to achieve serum topiramate concentrations comparable with those found in older children and adults. Enzyme-inducing comedication decreases serum topiramate concentration by approximately one-half and one-third in children and adults, respectively *(Battino et al, 2005)*.

Pharmacokinetics in the Elderly

A slow decline in renal function is associated with normal aging, with reductions in the glomerular filtration rate of 1% per year commonly noted after the fourth decade of life (particularly in men). In the absence of renal impairment however,

age alone (up to 70 years) had no effect on renal clearance or the elimination $t_{1/2}$ of topiramate in adults receiving topiramate *(Garnett, 2000; Sachdeo, 1998).*

Pharmacokinetic Interactions

Antiepileptic drugs

Potential interactions between topiramate and the concomitantly administered antiepileptic drugs carbamazepine, phenytoin, phenobarbital, and valproic acid were assessed in a number of open-label, pharmacokinetic studies in patients with partial epilepsy. In general, topiramate did not affect the pharmacokinetic profile of carbamazepine, phenobarbital or primidone, or valproate. A small decrease in phenytoin clearance may occur in some patients due to the addition of topiramate, causing an increase (of ~25%) in phenytoin plasma concentrations *(Bourgeois, 1996; Langtry et al, 1997; Bialer et al, 2004; Perucca, 2005)*.

Topiramate is an inhibitor of the cytochrome P450 enzyme CYP2C19, but does not affect CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1 or CYP3A4. Thus, in patients with refractory partial epilepsy, add-on therapy with topiramate did not appreciably affect the pharmacokinetic profile of concurrently administered carbamazepine (or carbamazepine-10,11-epoxide), phenobarbital or primidone.

In a study, the potential pharmacokinetic interactions between topiramate and **phenytoin** were evaluated in patients with epilepsy by studying their pharmacokinetics after monotherapy and concomitant topiramate/ phenytoin treatment *(Sachdeo et al, 2002)*. In nine of the 12 patients, phenytoin plasma concentrations remained stable, with a mean (± SD) area under the curve (AUC) ratio (combination therapy/monotherapy) of 1.13 ± 0.17 (range: 0.89-1.23). Three patients had AUC ratios of 1.25, 1.39, and 1.55, respectively, and with the addition of topiramate (800, 400, and 400 mg daily, respectively), their peak phenytoin plasma concentrations increased from 15 to 21 mg/L, 28 to 36 mg/L, and 27 to 41 mg/L, respectively. Human liver microsomal studies with S-mephenytoin showed that topiramate partially inhibited CYP2C 19 at very high concentrations of 300 µM (11% inhibition) and 900 µM (29% inhibition). Such high plasma concentrations would correspond to doses in humans that are 5 to 15 times higher than the recommended dose (200-400 mg). topiramate clearance was approximately twofold higher during concomitant topiramate/phenytoin therapy. This study provides evidence that the addition of topiramate to phenytoin generally does not cause clinically significant p interaction. Phenytoin induces the metabolism of topiramate, causing increased topiramate clearance, which may require topiramate dose adjustments when phenytoin therapy is added or is discontinued. topiramate may affect phenytoin concentrations in a few patients because of inhibition by topiramate of the CYP2C19-mediated minor metabolic pathway of phenytoin *(Sachdeo et al, 2002)*.

In a study, the influence of enzyme-inducing comedication and **valproic acid** on topiramate pharmacokinetics and metabolism at steady state was compared *(Nimrod et al, 2005)*. No significant differences were found in topiramate oral (CL/F) and renal (CLr) clearance between the valproic acid group and the control group. Mean topiramate CL/F and CLr were higher in the carbamazepine group than in controls (2.1 vs. 1.2 L/h and 1.1 vs. 0.6L/h, respectively; $p < 0.05$). In all groups, the urinary recovery of unchanged topiramate was extensive and accounted for 42–52% of the dose ($p > 0.05$). Urinary recovery of 2,3-O-des-

isopropylidene-topiramate (2,3-diol-topioramate) accounted for 3.5% of the dose in controls, 2.2% in the valproic acid group (p >0.05), and 13% in the carbamazepine group (p <0.05). The recovery of 10-hydroxy-topiramate (10-OH-topiramate) was twofold higher in the carbamazepine group than in controls, but it accounted for only <2% of the dose. The plasma concentrations of topiramate metabolites were several fold lower than those of the parent drug. Renal excretion remains a major route of topiramate elimination, even in the presence of enzyme induction. The twofold increase in topiramate-CL/F in patients taking carbamazepine can be ascribed, at least in part, to stimulation of the oxidative pathways leading to formation of 2,3-diol-topiramate and 10-OH-topiramate. valproic acid was not found to have any clinically significant influence on topiramate pharmacokinetic and metabolic profiles *(Nimrod et al, 2005).*

In contrast, valproic acid mean plasma concentrations and AUC 12 decreased by 11 % and its CL/F increased by 13% during concomitant topiramate 200 to 800 mg/day administration compared with values during monotherapy (all changes p <0.05). The investigators considered that these changes would be unlikely to be of clinical significance. During concomitant topiramate treatment, phenytoin AUC values in 6 of 12 patients increased to 125% of those observed during monotherapy; plasma phenytoin concentrations may, therefore, require monitoring during concomitant topiramate use *(Rosenfeld et al, 1997a)*.

Coadministration of **carbamazepine**, phenytoin or valproic acid with topiramate produced changes in topiramate pharmacokinetics that were consistent with metabolic changes resulting from cytochrome P450 enzyme induction. During concomitant carbamazepine 900 to 2400 mg/day and topiramate 5800 mg/day, topiramate AUC, C_{max} and minimum plasma concentrations were all ≈40% lower than during topiramate monotherapy, and topiramate CL/F and nonrenal clearance were 2- and 3-fold higher, respectively; CL/F was unaffected. Similarly, coadministration of phenytoin (dosage 260 to 600 mg/day) and topiramate (up to 800 mg/day) resulted in higher CL/F (2- to 3-fold) and lower AUC and C_{max} values (both 2- to 3-fold) of topiramate. The C_{max} and AUC_{12} of topiramate were also 18% higher during topiramate monotherapy than during concomitant valproic acid (dosage not stated); CL/F was 13% lower during monotherapy, but no difference in topiramate CLR was observed *(Britzi et al, 2005).*

In a study, to determine at steady state (in the same group of patients): (a) the pharmacokinetics of **lamotrigine** with lamotrigine monotherapy, (b) the pharmacokinetics of lamotrigine concomitantly administered with topiramate at three escalating topiramate doses (100, 200, and 400 mg/day), (c) the pharmacokinetics of topiramate at three escalating topiramate doses while receiving fixed-dose lamotrigine therapy, and (d) the pharmacokinetics of topiramate with topiramate monotherapy. The exposure, or area under the plasma lamotrigine concentration-time curve within a dosing interval at steady state (AUC_{ss}), did not change in the presence of topiramate, with mean AUC_{ss} values ranging at each topiramate dose level between 66 and 81 mg x h/L with concomitant lamotrigine/topiramate therapy compared with 77 mg x h/L with lamotrigine monotherapy. No significant change was found in the steady-state peak (C_{max}) and trough (C_{min}) plasma levels of lamotrigine in the presence and absence of topiramate. The mean (± SD) oral clearance (CL/F) of topiramate (400 mg/day) was 2.6 ± 1.1 L/h when given alone and 2.7 ± 0.7 L/h when given with lamotrigine. The similarity of CL/F values also was reflected by the similar exposure (AUC_{ss}), C_{max}, and C_{min} values of topiramate in the absence, and

presence of lamotrigine. The results of this study show that no pharmacokinetic interaction between topiramate and lamotrigine was observed at the doses used in this study *(Doose et al, 2003)*.

When topiramate was concomitantly administered with enzyme-inducing antiepileptic drugs, such as **phenobarbital**, the proportion of topiramate metabolized by the liver increases resulting in a shorter half-life and a higher total clearance (*Hachad et al, 2002*).

Oral contraceptives

Twelve women receiving stable valproic acid monotherapy for epilepsy received a combination norethindrone 1.0 mg/ethinyl estradiol 35-µg tablet daily for 21 days followed by seven daily doses of inert tablets for four 28-day cycles. After a baseline cycle (cycle I), topiramate 100, 200, and 400 mg every 12 h was administered in cycles 2 through 4, respectively. Compared with cycle 1, none of the norethindrone pharmacokinetic parameters changed significantly in the presence of topiramate, 100-400 mg every 12 h. Individual patient serum progesterone concentrations measured during each cycle were at or close to the limit of quantification with no apparent differences among cycles. However, mean AUC_{0-24} values for ethinyl estradiol were 18-30% lower in cycles 2 through 4 compared with cycle 1 ($p<0.05$ for all pairs), whereas mean oral serum clearance (CL/F) values were 14.7-33.0% higher ($p <0.05$ for cycles 2 and 4 vs. cycle 1). Mean t_{max} values determined during topiramate therapy were not significantly different from those at baseline *(Rosenfeld et al, 1997b)*.

In another study the pharmacokinetics of a combination oral contraceptive containing norethindrone and ethinyl estradiol during oral contraceptive monotherapy, concomitant oral contraceptive and topiramate therapy, and concomitant oral contraceptive and carbamazepine therapy was evaluated in order to comparatively evaluate the pharmacokinetic interaction, which may cause contraceptive failure. This randomized, open-label, five-group study included two 28-day cycles. Five groups of female subjects received oral doses of ORTHO-NOVUM 1/35 alone (cycle 1) and then concomitant with topiramate or carbamazepine (cycle 2). The treatment groups were group 1, topiramate, 50 mg/day; group 2, topiramate, 100 mg/day; group 3, topiramate, 200 mg/day; group 4, topiramate, 200 mg/day (obese women); and group 5, carbamazepine, 600 mg/day. Group 4 comprised obese women whose body mass index (BMI) was between 30 and 35 kg/m². The BMI of the remaining four groups was $\leq$27 kg/m². Coadministration of topiramate at daily doses of 50, 100, and 200 mg (nonobese) and 200 mg (obese) nonsignificantly ($p >0.05$) changed the mean AUC of ethinyl estradiol by -12%, +5%, -11 %, and -9%, respectively, compared with oral contraceptive monotherapy. A similar nonsignificant difference was observed with the plasma levels and AUC values of norethindrone ($p >0.05$). Carbamazepine (600 mg/day) significantly ($p <0.05$) decreased the AUC values of norethindrone and ethinyl estradiol by 58% and 42%, respectively, and increased their respective oral clearance by 69% and 127% ($p <0.05$). Because carbamazepine induces CYP 3A-mediated and glucuronide conjugation metabolic pathways, the significant increase in the oral clearance of ethinyl estradiol and norethindrone was anticipated. Topiramate, at daily doses of 50-200 mg, does not interact with an oral contraceptive containing norethindrone and ethinyl estradiol. The lack of the topiramate-oral contraceptive interaction is notable when it is

compared with the carbamazepine-oral contraceptive interaction *(Doose et al, 2003a)*.

Digoxin

Digoxin C_{max} and AUC values after a single oral 0.6 mg dose were reduced (by 16 and 12%; $p < 0.05$) and CL/F was increased by 13% ($p < 0.05$) when the drug was administered to 12 healthy volunteers pretreated with topiramate 200 mg/day for 6 days compared with administration of digoxin alone. Topiramate did not significantly alter the CLR (8% increase) or $t_{1/2\beta}$ (7.4% decrease) of digoxin. The effects of digoxin on topiramate pharmacokinetics were not tested.

Other Drug Interactions

CNS Depressants: Concomitant administration of topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. 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 caution if used in combination with alcohol and other CNS depressants.

Lithium: In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26% for AUC) following topiramate doses of up to 600 mg/day *(Bialer et al, 2004)*. Lithium levels should be monitored when co-administered with topiramate *(SPC, Topamax®, 2015)*

Hydrochlorothiazide (HCTZ): A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24 h) and topiramate (96 mg q12 h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of 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: A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin 500 mg b.d. and topiramate 100 mg b.d. in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean $AUC_{0\text{-}12h}$ increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. 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: A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glibenclamide: A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glibenclamide AUC_{24} during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glibenclamide (M1) and 3-cis-hydroxyglibenclamide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glibenclamide.

Topiramate, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis *(Dell'Orto et al, 2013)*. While using topiramate, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation. The interaction with benzodiazepines has not been studied. Concomitant administration of topiramate and valproic acid has been associated with hyperammonaemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. An association of hyperammonaemia with topiramate monotherapy or concomitant treatment with other antiepileptics has not been established.

Additional Pharmacokinetic Drug Interaction Studies: Clinical studies have been conducted to assess the potential pharmacokinetic drug interaction between topiramate and other agents. The changes in C_{max} or AUC as a result of the interactions are summarized below *(SPC, Topamax®, 2015).*

Concomitant Drug	Concomitant Drug Concentration	Topiramate Concentration
Amitriptyline	no change 20% increase in C_{max} and AUC of nortriptyline metabolite	not studied
Dihydroergotamine	no change	no change
Haloperidol	no change 31% increase in AUC of	16% increase in C_{max} , 17% increase in AUC

	the reduced metabolite	(80 mg propranolol q12 h)
Propranolol		
Sumatriptan	no change	not studied
Pizotifen	no change	no change

2.5.3.2. Pharmacodynamics

In Vitro Studies

Preclinical studies indicate that topiramate has at least four mechanisms of action that may contribute to its anticonvulsant activity. These include the following:

- Blockade of voltage-dependent Na^+ channels: Micromolar concentrations of topiramate reduced the duration and frequency of action potentials associated with sustained repetitive firing in cultured rat hippocampal neurons displaying spontaneous activity. Topiramate also blocked action potentials induced by depolarizing electric currents *(Zona et al, 1997)*.
- GABA potentiation: In cultured murine cerebellar granule cells, micromolar concentrations of topiramate in combination with gamma-aminobutyric acid (GABA) augmented GABA-stimulated chloride flux into chloride-depleted neurons compared to GABA alone (i.e., enhanced inhibitory neurotransmission) (*White et al, 1997; White et al, 2000*). The effect of topiramate on GABA, receptors was not blocked by the benzodiazepine antagonist flumazenil, suggesting that a novel or nonbenzodiazepine modulatory site is involved.
- Antagonism of a kainate subtype of the glutamate receptor: In other studies, topiramate produced concentration-dependent decreases in kainate-evoked inward currents (excitatory currents) in cultured hippocampal neurons, without affecting the activity of glutamate receptors of the N-methyl-D-aspartate (NMDA) subtype (those modulated by benzodiazepines) *(Gibbs et al, 2000; Skradski & White, 2000).*
- Inhibition of erythrocyte carbonic anhydrase: topiramate's sulfamate moiety is structurally similar to the carbonic anhydrase inhibitor acetazolamide, but topiramate's potency as an inhibitor of erythrocyte carbonic anhydrase is much lower than that of acetazolamide. In vitro, topiramate does not appear to exert an anticonvulsant effect through inhibition of carbonic anhydrase *(Shank et al, 1994)*.

In Vivo Studies

Topiramate blocked maximal electroshock seizures (MES) in rats and mice with potency similar to that of phenytoin, carbamazepine, phenobarbital, and acetazolamide *(Shank et al, 1994).* In the subcutaneous pentylenetetrazole test, topiramate, like phenytoin, was either ineffective or only weakly effective in mice and rats but increased seizure threshold in response to an intravenous pentylenetetrazole infusion in mice *(White et al, 1997)*. Topiramate was effective in inhibiting or blocking seizures in four other rodent models of epilepsy, including amygdala-kindled seizures in rats, sound-induced clonic seizures in the DBM2 mouse, tonic and absence-like seizures in the spontaneously epileptic rat, and seizures in a rat model of post-traumatic epilepsy. This profile of activity in experimental models of epilepsy suggests that topiramate may possess a broad spectrum of therapeutic action.

Topiramate has a high protective index (PI). The PI is determined from the ratio of the toxic dose$_{50}$ (TD_{50}) from a neurotoxicity test, such as the rotorod test or the loss of righting reflex test, to the MES effective dose$_{50}$. A higher, more advantageous ratio was obtained in rats and mice with topiramate than with phenytoin, carbamazepine, or phenobarbital. For example, with oral doses the PI for topiramate in rats was >116, whereas the values for phenobarbital, carbamazepine, and phenytoin were 3.5, 20.8, and >60.8, respectively *(White et al, 1997)*.

Pharmacodynamic Interactions

Perhaps the most clinically significant pharmacodynamic interaction is that of lamotrigine and valproic acid; these drugs exhibit synergistic efficacy when coadministered in patients with refractory partial and generalised seizures *(Patsalos et al, 2002).*

The combination of phentermine and extended release topiramate (phentermine/topiramate ER) has been approved for the treatment of obesity in conjunction with a lifestyle intervention. Combination phentermine/topiramate ER is associated with greater weight loss compared to its constituent monotherapy, with a more favourable adverse effect profile. Phentermine/topiramate ER also appears to have beneficial effects on cardiometabolic risk, although longer-term cardiovascular safety data are required. While there are no head-to-head studies among the currently available obesity pharmacotherapy agents, phentermine/ topiramate ER appears to have a superior weight loss profile *(Sweeting et al, 2014)*.

2.5.4. Overview of Efficacy

Efficacy in Epilepsy

The results of controlled clinical trials established the efficacy of topiramate as adjunctive therapy in adults and paediatric 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.

Efficacy in Patients with Partial Onset Seizures

In a study topiramate as monotherapy was evaluated in adults and children with recently diagnosed, localization-related epilepsy, comparing two dosages of topiramate in a multicenter, randomized, double-blind study *(Gilliam et al, 2003)*. Adults and children (≥3 years of age) were eligible if the maximum interval since epilepsy diagnosis was 3 years and patients had one to six partial-onset seizures during a 3-month retrospective baseline. At study entry, patients (N = 252) were untreated or receiving one antiepileptic drug for less than 1 month. After randomization to 50 or 500 mg/d topiramate (25 or 200 mg/day if weight ≤50 kg), patients remained in the study until 4 months after the last patient was randomized or until patients met seizure-related exit criteria (e.g., had two seizures). The primary efficacy outcome was a univariate analysis of time-to-exit, which was time to second seizure in 96% of patients. Results: The time-to-exit (median, 422 days vs. 293 days) favoured the higher dose of topiramate, but this difference was not significant. When time-to-exit was analyzed with time-to-first-seizure as a covariate, the difference between dosage groups was significant ($p < 0.01$), reflecting the higher seizure-free rates (54% vs. 39%, $p < 0.02$) and longer time-to-first-seizure (median 317 days vs. 108 days; $p < 0.06$) in patients receiving 200 or 500 mg/day topiramate. Higher plasma concentration was associated with increased time-to-first seizure ($p < 0.01$). Dose-related adverse events included paresthesias, weight loss, diarrhoea, and hypoesthesia. The authors conclude that although the primary efficacy analysis was negative, time-to-exit analyses that included time-to-first-seizure as a covariate, between-group differences in seizure-free rates, and longer time-to-first-seizure with higher serum concentration provide evidence that topiramate is effective as monotherapy in patients with localization-related epilepsy.

In a double-blinded, randomized, concentration controlled study, examining adjunctive topiramate therapy, patients assigned to a target topiramate plasma level of 10.5 mg/L obtained better seizure control than those assigned to target levels of 2 mg/L and 19 mg/L. Patients with refractory partial seizures were randomized to 1 of the 3 target plasma levels (n=65). Topiramate doses were then titrated over 8 weeks to attain these levels. Not all patients obtained their target plasma levels. Median doses were 100 mg for the 2 mg/L group, 450 mg for the 105 mg/L group and 677 mg for the 19 mg/L group. Patients randomized to 10.5 mg/L reduced seizure frequency by 85% compared to 39% in the 2 mg/L group ($p=0.03$) and 39% in the 19 mg/L group ($p=0.05$). Of note, lower target plasma levels were associated with higher study completion rates (85% compared with 78% and 50% in the 2, 10.5 and 19 mg/L groups, $p=0.03$). The occurrence of adverse events also was dose-related. Further studies involving larger numbers of subjects are required to establish target therapeutic levels *(Christensen et al, 2003).*

In a multicentre, randomized, double-blind, placebo-controlled study the efficacy and safety of topiramate 6 mg/kg/day in children (age 2 to 16 years) as adjunctive therapy was evaluated for uncontrolled partial-onset seizures with or without secondarily generalized seizures *(Elterman et al, 1999).* Patients with at least six partial-onset seizures during the 8-week baseline phase were treated with either topiramate (n = 41) or placebo (n = 45) for 16 weeks. Topiramate-treated patients had a greater median percent reduction from baseline in average monthly partial-onset seizure rate than placebo-treated patients (33.1% versus 10.5%, p = 0.034), a greater proportion of treatment responders (i.e., patients with a ≥50% seizure rate reduction; 16 of 41 [39%] versus 9 of 45 [20%], p = 0.080), and patients with a ≥75% seizure rate reduction (7 of 41 [17%] versus 1 of 45 [2%], p = 0.019), and better parental global evaluations of improvement in seizure severity (p = 0.019). Emotional lability (12% versus 4%), fatigue (15% versus 7%), difficulty with concentration or attention (12% versus 2%), and forgetfulness/impaired memory (7% versus 0%) were more frequent among topiramate-treated than placebo-treated patients. Most treatment-emergent adverse events were mild or moderate in severity. No topiramate-treated patients discontinued the study due to adverse events. Topiramate was safe and effective in the treatment of partial-onset seizures in children.

A multicentre, double-blind, randomized, parallel, placebo-controlled trial was conducted in 190 patients to evaluate the safety and efficacy of three dosages of topiramate (600, 800, and 1,000 mg/day) as adjunctive therapy for patients with refractory partial epilepsy *(Privitera et al, 1996).* During an 18-week double-blind treatment period, median percent reductions from baseline in average monthly seizure rates were 1% for placebo, 41% for topiramate 600 mg/day and topiramate 800 mg/day, and 384 for topiramate 1,000 mg/day. There was a 50% or greater reduction from baseline in seizure frequency in 9% of patients in the placebo group and in 44% for topiramate 600 mg/day, 40% for topiramate 800 mg/day, and 38% for topiramate 1,000 mg/day. No placebo patients were improved by 75 to 100% in seizure frequency, whereas 20% of the topiramate patients were improved to this degree. All intent-to-treat drug-placebo comparisons including seizure reduction, percent responders, and investigator and patient global evaluations significantly (p <0.02) favoured topiramate. Treatment-emergent adverse events consisted mainly of neurologic symptoms commonly observed during antiepileptic drug therapy. Sixteen percent of patients on topiramate discontinued therapy due to adverse events. Results of this study indicate that topiramate is a highly efficacious and generally well tolerated new antiepileptic drug. When large groups of patients are compared, incremental efficacy in the add-on setting is not observed at topiramate dosages above 600 mg/day; however, higher doses may prove beneficial to individual patients who tolerate them.

In a meta-analysis *(Reife et al, 2000)*, six double-blind, placebo-controlled trials were evaluated which were conducted with topiramate, initiated as adjunctive therapy in adults with treatment-resistant partial-onset seizures with or without secondary generalization. Because protocols and study populations were similar, data from the studies were pooled and analyzed for 527 patients treated with topiramate and 216 treated with placebo. Seizures were reduced 250% in 43% of topiramate-treated patients and in 12% of placebo-treated patients (p <0.001); 5% of topiramate-treated patients, but no placebo-treated patients, were seizure free during 11-1 9 weeks of double-blind treatment (p <0.001). The therapeutic effect was consistent regardless of seizure type, age, gender, baseline seizure rate, or

concomitant antiepileptic drug. With 100 mg/day topiramate as a starting dosage and weekly dosage increments of 100-200 mg/day added to maximally tolerated dosages of antiepileptic drugs, the most common treatment-emergent AEs were dizziness, somnolence, fatigue, psychomotor slowing, nervousness, paraesthesia, ataxia, memory difficulty and speech problems. These central nervous system effects were generally mild to moderate in severity, usually occurred early in treatment, often during titration, and resolved with continued treatment. Other notable treatment-emerged AEs were weight loss and, in a small percentage of patients, renal calculi.

A more recent meta-analysis evaluated the efficacy and safety of topiramate when used as an add-on treatment for people with drug-resistant partial epilepsy (*Pulman et al, 2014*). Randomised, placebo-controlled or active drug controlled add-on trials of topiramate (before 2013), recruiting people with drug-resistant partial epilepsy. Eleven trials were included, representing 1401 randomised participants. Baseline phases ranged from 4 to 12 weeks and double-blind phases from 11 to 19 weeks. The RR for a 50% or greater reduction in seizure frequency compared to placebo was 2.97 (95% CI 2.38 to 3.72). Dose regression analysis shows increasing effect with increasing dose, but found no advantage for doses over 300 or 400 mg per day. The RR for seizure freedom (95%CI) compared to placebo was 3.41 (95%CI 1.37 to 8.51). The RR for treatment withdrawal compared to placebo was 2.44 (95% CI 1.64 to 3.62). The RRs for the following side effects indicate that they are significantly associated with topiramate: ataxia 2.29 (99% CI 1.10 to 4.77); concentration difficulties 7.81 (2.08 to 29.29); dizziness 1.54 (99% CI 1.07 to 2.22); fatigue 2.19 (99% CI 1.42 to 3.40); paraesthesia 3.91 (1.51 to 10.12); somnolence 2.29 (99% CI 1.49 to 3.51); 'thinking abnormally' 5.70 (99% CI 2.26 to 14.38) and weight loss 3.47 (1.55 to 7.79). Evidence of publication bias was found (P value from the Egger test was P=0.003). They rated all studies included in the review as having either low or unclear risk of bias. Overall, they assessed the evidence as moderate quality due to the evidence of publication bias. The authors conclude that topiramate has efficacy as an add-on treatment for drug-resistant partial epilepsy in that it is three times more effective compared to a placebo in reducing seizures. However, the trials reviewed were of relatively short duration and provide no evidence for the long-term efficacy of topiramate. In the short term topiramate as an add-on has been shown to be associated with several adverse events. The results of this review cannot be extrapolated to monotherapy or treatment of other epilepsy types and future research should consider examining the effect of dose.

A meta-analysis assessed the effects of topiramate monotherapy versus carbamazepine monotherapy for epilepsy in people with partial-onset seizures (simple or complex partial and secondarily generalised) or generalised onset tonic-clonic seizures (with or without other generalised seizure types) (*Nevitt et al, 2017)*. They selected randomised controlled trials in children or adults with partial-onset seizures or generalised-onset tonic-clonic seizures with or without other generalised seizure types with a comparison of monotherapy with either topiramate or carbamazepine. This was an individual participant data (IPD) review. This was an individual participant data (IPD) review. IPD were available for 1151 of 1239 eligible individuals from two of three eligible studies (93% of the potential data). A small proportion of individuals recruited into these trials had 'unclassified seizures;' for analysis purposes, these individuals are grouped with

those with generalised onset seizures. For remission outcomes, a HR < 1 indicated an advantage for carbamazepine, and for first seizure and withdrawal outcomes, a HR < 1 indicated an advantage for topiramate. The main overall results, given as pooled HR adjusted for seizure type (95% CI) were: for time to withdrawal of allocated treatment 1.16 (0.98 to 1.38); time to first seizure 1.11 (0.96 to 1.29); and time to 6-month remission 0.88 (0.76 to 1.01). There were no statistically significant differences between the drugs. A statistically significant advantage for carbamazepine was shown for time to 12-month remission: 0.84 (0.71 to 1.00). The results of this review are applicable mainly to individuals with partial-onset seizures; 85% of included individuals experienced seizures of this type at baseline. For individuals with partial-onset seizures, a statistically significant advantage for carbamazepine was shown for time to withdrawal of allocated treatment (HR 1.20, 95%CI 1.00 to 1.45) and time to 12-month remission (HR 0.84, 95% CI 0.71 to 1.00). No statistically significant differences were apparent between the drugs for other outcomes and for the limited number of individuals with generalised-onset tonic-clonic seizures with or without other generalised seizure types or unclassified seizures. The most commonly reported adverse events with both drugs were drowsiness or fatigue, 'pins and needles' (tingling sensation), headache, gastrointestinal disturbance and anxiety or depression The rate of adverse events was similar across the two drugs. They judged the methodological quality of the included trials generally to be good; however, there was some evidence that the open-label design of the larger of the two trials may have influenced the withdrawal rate from the trial. Hence, they judged the evidence for the primary outcome of treatment withdrawal to be moderate for individuals with partial-onset seizures and low for individuals with generalised-onset seizures. For efficacy outcomes (first seizure, remission), they judged the evidence from this review to be high for individuals with partial-onset seizures and moderate for individuals with generalised-onset or unclassified seizures. The authors conclude that for individuals with partial-onset seizures, there is evidence that carbamazepine is less likely to be withdrawn and that 12-month remission will be achieved earlier than with topiramate. No differences were found between the drugs in terms of the outcomes measured in the review for individuals with generalised tonic-clonic seizures with or without other seizure types or unclassified epilepsy; however, they encourage caution in the interpretation of these results due to the small numbers of participants with these seizure types.

Children with partial-onset seizures, with or without secondary generalization, participating in a double-blind, placebo-controlled trial of topiramate as adjunctive therapy were eligible to participate in an open-label, long-term extension study *(Ritter et al, 2000)*. A total of 83 children (mean age, 9 years) continued long-term open-label topiramate therapy in which the dosages of topiramate and concomitant antiepileptic drugs were adjusted according to clinical response (mean topiramate dosage, 9 mg/kg/day). Seizure frequency over the last 3 months of therapy was reduced 250% in 57% of children; 14% of children were seizure-free 2 6 months at the last visit. During treatment periods up to 2% years (mean, 15 months), 6% of children discontinued because of treatment-emergent adverse events; 13% discontinued because of inadequate seizure control. The authors conclude that topiramate is well tolerated and provides long-term seizure control in children with partial onset seizures.

Novotny et al (2010) evaluated the efficacy and safety of adjunctive topiramate (sprinkle capsules or oral liquid) in reducing daily rates of partial-onset seizures (POS) in infants with refractory POS. In this double-blind, placebo-controlled,

parallel-group, international study, infants (n = 149) with clinical or EEG evidence of refractory POS were randomly allocated (1:1:1:1) to receive adjunctive topiramate 5, 15, or 25 mg/kg/d or placebo for 20 days. The primary variable was the median percentage reductions in daily POS rate from baseline to final assessment as recorded on a 48-hour video-EEG. Of the 149 infants (mean age 12 months) included in the intent-to-treat analysis set, 130 completed the study. Median percentage reduction from baseline in daily POS rate was not significantly different (p = 0.97) between topiramate 25 mg/kg (20.4%) and placebo (13.1%). Lower doses were not formally tested, but nominal p values for comparisons with placebo were not significant (15-mg/kg/d dose: p = 0.97; 5-mg/kg/d dose: p = 0.91). Treatment-emergent fever, diarrhoea, vomiting, anorexia, weight decrease, somnolence, and viral infection occurred more frequently (≥10% difference) with topiramate than with placebo. In conclusion, in infants aged 1–24 months, topiramate 5, 15, or 25 mg/kg/d was not effective as adjunctive treatment for refractory partial-onset seizures. No new safety concerns associated with topiramate use were noted.

Ramsay et al (2008) compared two dosages of topiramate in a pilot study of patients ≥60 years of age with partial-onset seizures. In this 24-week, double-blind, randomized, parallel-group study, patients with one or more seizures in previous 6 months were randomized to treatment with 50 or 200 mg/day topiramate. Topiramate was initiated as monotherapy or added to one AED and titrated by 25 mg/day per week to target or maximum tolerated dose as the concomitant AED, if any, was withdrawn. Thirty-eight patients were randomized to the 50 mg/day topiramate (mean age, 68 years) and 39–200 mg/day topiramate (69 years). Seizure control was similar with the two dosages when topiramate could be used as monotherapy, whereas 200 mg topiramate was more effective than 50 mg in patients requiring adjunctive therapy. This pilot study supports the practice of using low-to-moderate dosages of AEDs in older adults.

Efficacy in Patients with Primary/Secondary Generalized Tonic-Clonic Seizure

The efficacy and safety of topiramate as adjunctive therapy for the treatment of primary generalized tonic-clonic (PGTC) seizures were investigated in a randomized, double-blind, placebo-controlled study *(Biton et al, 1999).* Eighty patients, 3 to 59 years old, who experienced three or more PGTC seizures during an 8-week baseline phase were randomly assigned to treatment with either topiramate (n = 39) or placebo (n = 41). Topiramate was titrated to target doses of approximately 6 mg/kg/day over 8 weeks and maintained for another 12 weeks. The median percentage reduction from baseline in PGTC seizure rate was 56.7% for topiramate patients and 9.0% for placebo patients (p = 0.019). The proportion of patients with 50% or higher reduction in PGTC seizure rate was 22/39 (56%) and 8/40 (20%) for the topiramate and placebo groups, respectively (p = 0.001). The median percentage reduction in the rate of all generalized seizures was 42.1% for topiramate patients and 0.9% for placebo patients (p = 0.003). The proportions of patients with 50% or higher reductions in generalized seizure rate were 18/39 (46%) and 7/41 (17%) for the topiramate and placebo groups, respectively (p = 0.003). The most common adverse events were somnolence, fatigue, weight loss, difficulty with memory, and nervousness. Treatment-limiting adverse events occurred in one patient in the topiramate group (anorexia and weight loss) and one in the placebo group (granulocytopenia and thrombocytopenia). The authors conclude that topiramate is well-tolerated and effective for the adjunctive treatment of PGTC seizures.

Topiramate inhibited recurrence of seizures in a 23-year-old woman who experienced a 4-minute generalized tonic-clonic seizure apparently caused by the clozapine therapy she was receiving. The patient had no personal history of seizures prior to receiving clozapine. When diagnosed with paranoid schizophrenia, she had initially been treated with risperidone (up to 6 mg/day), then olanzapine (up to 10 mg/day). She gained a significant amount of weight and exhibited evidence of negative symptoms of the psychosis and depressive symptoms. Despite beginning sertraline 100 mg/day, she attempted suicide and was hospitalized. The patient was switched from olanzapine to clozapine (increased by 50 mg every 4 days to a stable dose of 200 mg/day) and continued to receive sertraline. She had a favourable clinical response to the clozapine. Her tonic-clonic seizure occurred during the third week of clozapine treatment. It was decided that clozapine should be continued, and topiramate was added for inhibition of seizure activity (titrated from 50 to 200 mg/day). Over 6 months of follow-up, no evidence of seizures was observed clinically or on electroencephalography. No side effects of topiramate therapy occurred, and the patient had a slight decrease in body mass index *(Navarro et al, 2001).*

A total of 292 adult patients (mean age, 33 years) with partial and/or generalized seizures previously resistant to antiepileptic drug therapy (median baseline seizure rate, 12 seizures/month) were treated with open-label topiramate in dosages of 100-1,600 mg/day. The mean duration of topiramate treatment was 413 days (range, 84-804 days), and the mean topiramate dosage was 503 mg/day (range, 100-1,600 mg/day; median topiramate dosage, 300 mg/day). Seizure reduction was calculated from seizure counts during the last 3 months and last 6 months of topiramate therapy compared with baseline. Overall, >50% of patients achieved 250% seizure reduction. More important, 11% of patients were seizure-free for 23 months at the last visit; 10% of patients were seizure free for 26 months at the last visit. This robust therapeutic response was consistent for patients receiving topiramate dosages >400 and <400 mg/day. The most commonly reported AEs were related to the CNS. Over the 2.2-year treatment period, 19% of patients discontinued topiramate therapy because of inadequate seizure control; 32% discontinued because of adverse events. Findings from this study show that topiramate is a useful agent for long-term seizure control, with some patients becoming seizure free for extended periods despite failing previous antiepileptic drug therapy *(Abou-Khalil et al, 2000).*

Secondary generalized tonic–clonic seizures (SGTCS) are among the most severe forms of seizures, and the main risk factor for sudden unexpected death in epilepsy (SUDEP). *Hemery et al (2014)* performed a meta-analysis of randomized controlled trials of adjunctive AED in which information on efficacy outcomes (i.e., responder rate and/or frequency per 28 days relative to baseline) were available both for all seizure types and for SGTCS. The primary analysis evaluated the efficacy of AEDs on all types of seizure and on SGTCS by comparing the responder rates for AED and for placebo. Responder rate was available both for all seizure types and for SGTCS in 13 of the 72 eligible trials, evaluating 7 AEDs. Only three AEDs - lacosamide, perampanel and topiramate - showed greater efficacy than placebo. However, CIs of relative risks overlapped for all AEDs but pregabalin, which demonstrated significantly lower efficacy than lacosamide, perampanel, and topiramate. Moreover, there was a nonsignificant trend toward a lower relative risk of responder rate for SGTCS than for all seizure types, which appeared related to a greater response to placebo for this outcome. In conclusion, indirect comparison of AEDs using randomized placebo-controlled add-on trials does not support robust differences between AEDs to prevent SGTCS.

Efficacy in Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is a severe childhood epilepsy syndrome characterized by multiple seizure types and a specific abnormal EEG pattern. Mental retardation or regression is common, but may not always be present at the onset of the disease. The typical EEG pattern consists of generalized, slow spike-and-wave discharges often accompanied by other multifocal abnormalities. Although a number of seizure types can occur, those most commonly associated with this syndrome are tonic, atonic, and absence seizures. Because it is difficult at times for parents to differentiate tonic from atonic seizures, these types of seizures are combined in drug studies and called drop attacks. Lennox-Gastaut syndrome typically develops between 1 and 8 years of age, although its greatest frequency of initial onset occurs before 5 years of age. The long-term prognosis of Lennox-Gastaut syndrome is frequently poor, with deteriorating mental function and persistently high rates of seizures.

Adjunctive topiramate therapy was effective in reducing the number of drop attacks or tonic-atonic seizures associated with Lennox-Gastaut syndrome *(Sachdeo et al, 1999)*. In a double-blind trial, patients (age 1 to 30 years old) with Lennox-Gastaut syndrome were randomized to receive either topiramate (n=48) or placebo (n=50) as adjunctive therapy to their current antiepileptic therapy. Topiramate was initially administered as 1 mg/kg/day (mg/kg/day) twice daily. By the third week it was titrated up to 6 mg/kg/day. This dose or the maximal tolerated dosage was maintained for an 8-week maintenance period. The median average dosage of topiramate during the maintenance period was 5.8 mg/kg/day. The median percentage reduction in drop attacks form baseline in the average monthly seizure rate was significantly greater in the topiramate group as compared to the placebo group (14.8% versus 5.1%, $p = 0.041$). Parents also judged (utilizing a global evaluation) the children in the topiramate group as twice as likely to have a significant improvement in seizure severity ($p = 0.037$). When all seizures were reviewed (generalized and partial), there was no significant reduction in median percentage decline from baseline. However, when atypical absence seizures were excluded, the median percentage reduction in the average monthly seizure rate was 23.9% for topiramate and 2% for placebo. Common adverse effects in the topiramate group included somnolence, anorexia, nervousness, behavioural problems, fatigue, dizziness, and weight loss. This study suggests that topiramate is an important addition for the treatment of Lennox-Gastaut syndrome.

In a meta-analysis, the effects of pharmaceutical therapies used to treat Lennox-Gastaut syndrome were compared in terms of control of seizures and adverse effects *(Hancock & Cross, 2003)*. They searched the Cochrane Epilepsy Group's Specialized Register (March 2003), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2003), and MEDLINE (1966 to March 2003). EMBASE was also searched (1980 to March 2003). All randomised controlled trials (RCTs) of the administration of drug therapy to patients with Lennox-Gastaut syndrome were included. Data was independently extracted by two reviewers. Analysis included assessing study quality, as well as statistical analysis of the effects on overall seizure rates and effects on specific seizure types (e.g. drop attacks), adverse effects and mortality. They found five RCTs, but were unable to perform any sort of meta-analysis, because each trial looked at different populations, different therapies and considered different outcomes. The authors conclude that the optimum treatment for Lennox-Gastaut syndrome

remains uncertain and no study to date has shown any one drug to be highly efficacious; lamotrigine, topiramate and felbamate may be helpful as add-on therapy. Until further research has been undertaken clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects.

In a most recent review (*Ostendorf & Ng, 2017*), approved medications are: lamotrigine, topiramate, rufinamide, felbamate and clobazam have demonstrated efficacy in reducing seizure burden. However, currently approved antiseizure therapies have failed to provide long-lasting seizure control for most individuals with Lennox-Gastaut syndrome. Therapies under investigation include cannabinoids, fenfluramine and transcranial direct current stimulation

Migraine prophylaxis

Migraine headache is a neurologic disorder associated with significant disability and impaired quality of life, adversely affecting daily activity and work-related productivity for many persons. Approximately 11% of the population experiences migraine, in the industrialized countries. The goals of managing migraine are to reduce migraine frequency, severity, and disability; reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies; improve quality of life; reduce headache-related distress and psychologic symptoms; educate patients and enable them to manage their disease; and avoid dose escalation of acute medications. Recent studies suggest that habitual overuse of acute medications, including triptans, ergots, and other analgesics, can lead to the development of chronic daily headaches. Preventive medications can serve an important role in the treatment of migraine by reducing migraine frequency and by ameliorating dose escalation and the potential for overuse of acute pharmacotherapies.

Open-label trials and small controlled studies have reported topiramate's efficacy in migraine prevention. In a 26-week, randomized, double-blind, placebo-controlled study *(Silberstein et al, 2004)* the efficacy and safety of topiramate was assessed as a migraine-preventive therapy. Patients were aged 12 to 65 years, had a 6-month International Headache Society migraine history, and experienced 3 to 12 migraines per month, but had 15 or fewer headache days per month during the 28-day baseline period. Participants were randomized to placebo or topiramate, 50, 100, or 200 mg/day, titrated by 25 mg/week to the assigned dose or as tolerated in 8 weeks; maintenance therapy continued for 18 weeks. The primary efficacy assessment was a reduction in mean monthly migraine frequency across the 6-month treatment phase. Secondary end points were responder rate, time to onset of action, mean change in migraine days per month, and mean change in rescue medication days per month. Four hundred eighty-seven patients were randomized, and 469 composed the intent-to-treat population. The mean ± SD monthly migraine frequency decreased significantly for the 100 mg/day group (from 5.4 ± 2.2 to 3.3 ± 2.9; P<0.001) and the 200 mg/day group (from 5.6 ± 2.6 to 3.3 ± 2.9; P<0.001) vs. the placebo group (from 5.6 ± 2.3 to 4.6 ± 3.0); improvements occurred within the first treatment month. Significantly more topiramate-treated patients (50 mg/day 35.9% [P=0.04]; 100 mg/day, 54.0% [P<0.001]; and 200 mg/d, 52.3% [P<0.001]) exhibited a 50% or more reduction in monthly migraine frequency than placebo-treated patients (22.6%). Adverse events included paraesthesia, fatigue, nausea, anorexia, and taste per version.

The authors conclude that topiramate, 100 or 200 mg/day, was effective as a preventive therapy for patients with migraine *(Silberstein et al, 2004)*.

In an other study, the objectives were to evaluate the efficacy and tolerability of topiramate, given at the dose of 100 mg/day, in the prophylactic treatment of migraine *(Mei et al, 2004)*. The hypothesis that migraine is the result of a condition of neuronal hyperexcitability and the quest for drugs that are able to limit the number of crises justifies the attempt to utilise the new antiepileptic drugs in the prophylaxis of this pathology, which is so important due to its high prevalence and due to the high disability it causes. The study was randomised double-blind versus placebo, lasting 16 weeks, and was preceded by a run-in period of 4 weeks. One hundred and fifteen patients were randomly allocated to treatment with topiramate or placebo: 35 patients completed the study in the topiramate group and 37 patients in the placebo group. At the end of the double-blind phase of study, in the topiramate group, they recorded a significant reduction in the frequency of migraine crises (from 5.26 at baseline to 2.60 in the last 4 weeks), a significant reduction in the quantity of symptomatic drugs taken as compared to the placebo control group (from 6.17±1.80 SD to 2.57±0.80) and a significant downward trend in the number of days of disability over the 16-week period of therapy. In the topiramate group, side effects were transient and well tolerated. Topiramate has thus proven its efficacy and tolerability in the prophylaxis of migraine *(Mei et al, 2004)*.

In a large controlled trial the efficacy and safety of topiramate was assessed for migraine prevention *(Brandes et al, 2004)*. It was a 26-week, randomized, double-blind, placebo-controlled study was conducted during outpatient treatment at 52 North American clinical centres. Patients were aged 12 to 65 years and had a 6-month history of migraine (International Headache Society criteria) and 3 to 12 migraines a month but no more than 15 headache days a month during a 28-day prospective baseline phase. After a washout period, patients meeting entry criteria were randomized to topiramate (50, 100, or 200 mg/day) or placebo. Topiramate was titrated by 25 mg/week for 8 weeks to the assigned or maximum tolerated dose, whichever was less. Patients continued receiving that dose for 18 weeks. The primary efficacy measure was change from baseline in mean monthly migraine frequency. Secondary efficacy measures included responder rate (proportion of patients with $\geq$50% reduction in monthly migraine frequency), reductions in mean number of monthly migraine days, severity, duration, and days a month requiring rescue medication, and adverse events. The month of onset of preventive treatment action was assessed. Of 483 patients randomized, 468 provided at least 1 postbaseline efficacy assessment and comprised the intent-to-treat population. Mean monthly migraine frequency decreased significantly for patients receiving topiramate at 100 mg/day (−2.1, P=0.008) and topiramate at 200 mg/day (−2.4, P<0.001) vs. placebo (−1.1). Statistically significant reductions (P < 0.05) occurred within the first month with topiramate at 100 and 200 mg/day. The responder rate was significantly greater with topiramate at 50 mg/d (39%, P = 0.01), 100 mg/day (49%, P < 0.001), and 200 mg/day (47%, P < 0.001) vs. placebo (23%). Reductions in migraine days were significant for the 100 mg/day (P = 0.003) and 200-mg/day (P < 0.001) topiramate groups. Rescue medication use was reduced in the 100 mg/day (P = 0.01) and 200 mg/day (P = 0.005) topiramate groups. Adverse events resulting in discontinuation in the topiramate groups included paraesthesia, fatigue, and nausea. The authors conclude that topiramate showed significant efficacy in migraine prevention within the first

month of treatment, an effect maintained for the duration of the double-blind phase *(Brandes et al, 2004)*.

In a meta-analysis the evidence from controlled trials on the efficacy and tolerability of anticonvulsants was assessed for preventing migraine attacks in adult patients with migraine *(Chronicle & Mulleners, 2004)*. They searched PubMed (1966-December 2005), EMBASE (1974-December 2005) and the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2005), and hand searched Headache and Cephalalgia through April 2006. Studies were required to be prospective, controlled trials of anticonvulsant drugs taken regularly to prevent the occurrence of migraine attacks and/or to reduce the intensity of those attacks. Studies were selected and data extracted by two independent reviewers. For migraine frequency data, standardized mean differences (SMDs) were calculated for individual studies and pooled across studies. For dichotomous data on significant reduction in migraine frequency, odds ratios (ORs) and numbers-needed-to-treat (NNTs) were similarly calculated. Adverse events were analyzed by calculating numbers-needed-to-harm (NNHs) for studies using similar agents. Twenty-three papers met the inclusion criteria. In total, data from 2927 patients were considered. Analysis of data from 10 trials (n = 902) demonstrates that anticonvulsants, considered as a class, reduce migraine frequency by about 1.3 attacks per 28 days as compared to placebo (WMD -1.31; 95% confidence interval [CI] -1.99 to -0.63). Data from 13 trials (n = 1773) show that anticonvulsants, considered as a class, also more than double the number of patients for whom migraine frequency is reduced by 50% or more relative to placebo (RR 2.25; 95% CI 1.79 to 2.84; NNT 3.9; 95% CI 3.4 to 4.7). For six trials of sodium valproate and divalproex sodium, NNHs for five clinically important adverse events ranged from 7.0 to 18.8. For six trials of topiramate, NNHs for seven adverse events (100 mg dose) ranged from 2.4 to 31.2. The authors conclude that anticonvulsants appear to be both effective in reducing migraine frequency and reasonably well tolerated. There is noticeable variation among individual agents, but there are insufficient data to know whether this is due to chance or variation in true efficacy. Acetazolamide, clonazepam, lamotrigine and vigabatrin were not superior to placebo (one trial each). Relatively few robust trials are available for agents other than sodium valproate/divalproex sodium and topiramate; gabapentin in particular needs further evaluation. Trials designed with sufficient power to compare different drugs are also necessary.

In a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group study, *Dodick et al (2009)* compared the efficacy and tolerability of topiramate and amitriptyline in the prophylaxis of episodic migraine headache. In this noninferiority study, topiramate was at least as effective as amitriptyline in terms of reducing the rate of mean monthly migraine episodes and all prespecified secondary efficacy end points. Topiramate was associated with improvement in some quality-of-life indicators compared with amitriptyline and was associated with weight loss and improved weight satisfaction.

In a randomized, double-blind, placebo-controlled, multicenter clinical trial, *Silberstein et al (2009)* evaluated prespecified secondary endpoints to define the utility of topiramate in the treatment of chronic migraine. In addition to significantly reducing mean monthly migraine/migrainous and migraine headache days, treatment of chronic migraine with topiramate was effective with regard to several traditionally important and clinically relevant secondary outcomes in migraine

prevention trials. Treatment with topiramate was well tolerated and not associated with serious adverse events.

Cady et al (2012) compared the efficacy and clinical benefit of migraine prevention using pre-emptive frovatript and daily topiramate. The number of migraine attacks and headache days per month decreased significantly from baseline for both groups. Though this study was not powered to directly compare the efficacy of the 2 drugs, topiramate showed superiority over frovatriptan at Month 2 in reduction of headache days, which was a secondary end point in the study (P = 0.036).

A randomized, one-year clinical trial compared the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis (*Luo et al, 2012*). The proportion whose monthly headache frequency decreased more than 50% was 66.7% (26/39) in the flunarizine group, 72.7% (32/44) in the topiramate group and 76.7% (33/43) in the combination group, respectively (P = 0.593). The mean monthly days and severity of headache in the three groups also declined and was more significant in the flunarizine plus topiramate group than in the flunarizine group and the topiramate group (P < 0.05). In the flunarizine group, the average weight change was 0.6 kg. Topiramate was associated with a mean weight loss was of -0.9 kg in the topiramate group and -0.2 kg in the flunarizine plus topiramate group. In conclusion, flunarizine, topiramate, and the combination of flunarizine with topiramate are all effective and have good tolerability in migraine prophylaxis. Adding topiramate to flunarizine may reduce the latter's impact on body weight.

The multicentre, randomized, double-blind, placebo-controlled INTREPID study evaluated whether topiramate prevents development of chronic daily headache (CDH) in adult subjects with high-frequency episodic migraine. A secondary objective was to assess the efficacy of topiramate as preventive migraine treatment in this population (*Lipton et al, 2011*). Topiramate 100 mg/day did not prevent the development of CDH at six months. Topiramate was effective in reducing headache days and migraine headache days and generally well tolerated.

A meta-analysis (*Linde et al, 2013*) assessed the evidence from controlled trials on the efficacy and tolerability of topiramate for preventing migraine attacks in adult patients with episodic migraine. Twenty papers describing 17 unique trials met the inclusion criteria. Analysis of data from nine trials (1737 participants) showed that topiramate reduced headache frequency by about 1.2 attacks per 28 days as compared to placebo (MD -1.20; 95% CI -1.59 to -0.80). Data from nine trials (1190 participants) show that topiramate approximately doubled the proportion of responders relative to placebo (RR 2.02; 95% CI 1.57 to 2.60; NNT 4; 95% CI 3 to 6). Separate analysis of different topiramate doses produced similar MDs versus placebo at 50 mg (-0.95; 95% CI -1.95 to 0.04; three studies; 520 participants), 100 mg (-1.15; 95% CI -1.58 to -0.71; six studies; 1620 participants), and 200 mg (-0.94; 95% CI -1.53 to -0.36; five studies; 804 participants). All three doses significantly increased the proportion of responders relative to placebo; ORs were as follows: for 50 mg, 2.35 (95% CI 1.60 to 3.44; three studies; 519 participants); for 100 mg, 3.49 (95% CI 2.23 to 5.45; five studies; 852 participants); and for 200 mg, 2.49 (95% CI 1.61 to 3.87; six studies; 1025 participants). All three doses also significantly improved three or more domains of quality of life as compared to placebo. Meta-analysis of the three

studies that included more than one dose of topiramate suggests that 200 mg is no more effective than 100 mg. With regard to mean headache frequency and/or responder rate, seven trials using active comparators found (a) no significant difference between topiramate and amitriptyline (one study, 330 participants); (b) no significant difference between topiramate and flunarizine (one study, 83 participants); (c) no significant difference between topiramate and propranolol (two studies, 342 participants); (d) no significant difference between topiramate and relaxation (one study, 61 participants); but (e) a slight significant advantage of topiramate over valproate (two studies, 120 participants). Relaxation improved migraine-specific quality of life significantly more than topiramate. In trials of topiramate against placebo, seven adverse events (AEs) were reported by at least three studies. These were usually mild and of a non-serious nature. Except for taste disturbance and weight loss, there were no significant differences in the frequency of AEs in general, or of the seven specific AEs, between placebo and topiramate 50 mg. AEs in general and all of the specific AEs except nausea were significantly more common on topiramate 100 mg than on placebo, with NNHs varying from 3 to 25, and the RDs versus placebo were even higher for topiramate 200 mg, with NNHs varying from 2 to 17. This meta-analysis demonstrates that topiramate in a 100 mg/day dosage is effective in reducing headache frequency and reasonably well tolerated in adult patients with episodic migraine. This provides good evidence to support its use in routine clinical management. More studies designed specifically to compare the efficacy or safety of topiramate versus other interventions with proven efficacy in the prophylaxis of migraine are needed.

Conclusion: Based on randomized controlled trials, topiramate reduces migraine frequency and acute medication use, improves quality of life, and reduces disability in patients with episodic migraine and in those with chronic migraine with or without medication overuse headache.

Efficacy in Paediatric Population

A study evaluated the efficacy and safety of topiramate for migraine prevention in adolescents (*Lewis et al, 2009*). A total of 29 (83%) of 35 subjects treated with topiramate at 50 mg/day, 30 (86%) of 35 subjects treated with topiramate at 100 mg/day, and 26 (79.0%) of 33 placebo-treated subjects completed double-blind treatment. Topiramate at 100 mg/day, but not 50 mg/day, resulted in a statistically significant reduction in the monthly migraine attack rate from baseline versus placebo (median: 72.2% vs. 44.4%) during the last 12 weeks of double-blind treatment. Topiramate at 100 mg/day, but not 50 mg/day, also resulted in a statistically significant reduction in the monthly migraine day rate from baseline versus placebo. The responder rate favoured topiramate at 100 mg/day (83% vs. 45% for placebo). Upper respiratory tract infection, paraesthesia, and dizziness occurred more commonly in the topiramate groups than in the placebo group. In conclusion, the 100 mg/day topiramate group demonstrated efficacy in the prevention of migraine in paediatric subjects. Overall, topiramate treatment was safe and well tolerated.

The double-blinded, placebo-controlled CHAMP study compared the effectiveness of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine (*Powers et al, 2017*). There were no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or

placebo over a period of 24 weeks. The active drugs were associated with higher rates of adverse events.

Efficacy in other indications (not included in SPC)

Topiramate has been evaluated in a number of neurologic and psychiatric conditions, such as trigeminal neuralgia, essential tremor, diabetic neuropathy, binge-eating disorder, schizophrenia, and bipolar disorders, etc.

2.5.5. Overview of Safety

The short-term safety profile of topiramate was evaluated in a series of double-blind, placebo-controlled trials among patients with refractory partial epilepsy in which topiramate was studied at dosages of 200 to 1000 mg/day. The most common treatment-emergent adverse events in these studies were related to the CNS: dizziness, somnolence, abnormal thinking, fatigue, ataxia, confusion, paraesthesia, impaired concentration, agitation, amnesia, speech disorders, aphasia, and anorexia.

Chronic AEs were evaluated in the larger topiramate database. The late AEs included psychosis or depression, weight loss, and nephrolithiasis. Depression occurred in 15% (usually during the first 3 months of treatment) and psychosis in 3% (generally late in the course) of patients in non-comparative trials. Acute psychotic symptoms have been also reported soon after initiation of topiramate therapy. These rates of occurrence are comparable to those reported in epidemiologic studies of patients with epilepsy. Weight reduction observed during topiramate therapy appeared to be dose-related, with mean decreases ranging from 1.1 kg in patients receiving 200 mg/day of topiramate to 5.9 kg in patients receiving > 800 mg/day. Body weight loss (occurring in up to 78% of patients) was also more common in heavier patients, women, and those patients receiving concomitant therapy with valproate. Weight reduction typically began within the first 3 months of treatment and peaked approximately after 9 to 15 months of therapy; weight loss was considered to be a "positive" adverse event by many patients. Nephrolithiasis occurred in 1.5% of 1200 patients receiving topiramate in non-comparative trials; this incidence is similar to that reported during acetazolamide therapy. Stones occurred only in male patients and were passed spontaneously in 67% of cases. Seventy-eight percent of subjects with topiramate-induced nephrolithiasis elected to continue topiramate treatment after passing the stone. Stone formation is believed to be related to an increase in urinary pH and reduced excretion of citrate associated with topiramate's carbonic anhydrase-inhibitory activity. No clinically important changes or consistent alterations in clinical laboratory values or other safety measurements were observed in either placebo-controlled or noncomparative studies. As for any other new antiepileptic drug, the number of exposures to topiramate is not yet large enough to exclude rare idiosyncratic reactions *(Michelucci et al, 1998).*

Adverse Effects

Since topiramate has most frequently been co-administered with other antiepileptic agents, it is not possible to determine which agents, if any, are associated with AEs. In double blind clinical trials, some of which included a rapid titration period, AEs which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated adult patients than in placebo included: abdominal pain, ataxia, anorexia, asthenia, confusion, difficulty with concentration/attention, difficulty with memory, diplopia, dizziness, fatigue, language problems, nausea, nystagmus, paraesthesia, psychomotor slowing, somnolence, speech disorders/related speech problems, abnormal vision and weight decrease. Topamax may cause agitation and emotional lability (which may manifest mood problems and nervousness) and depression. Other less common AEs include, gait abnormal, aggressive reaction, apathy, cognitive problems, co-ordination problems, leucopenia, psychotic symptoms (such as hallucinations) and taste perversion. Isolated cases of venous thromboembolic events have been

reported. A causal association with the drug has not been established. Reports of increases in liver enzymes in patients taking topiramate with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with topiramate.

In double blind clinical trials in children, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated children than in placebo included: somnolence, anorexia, fatigue, insomnia, nervousness, personality disorder (behaviour problems), difficulty with concentration/attention, aggressive reaction, weight decrease, gait abnormal, mood problems, ataxia, saliva increased, nausea, difficulty with memory, hyperkinesia, dizziness, speech disorders/related speech problems and paraesthesia. AEs that occurred less frequently but were considered potentially medically relevant included: emotional lability, agitation, apathy, cognitive problems, psychomotor slowing, confusion, hallucination, depression and leucopenia.

Hyperammonaemia is an uncommon side effect of topiramate that has only been reported when it is used as an adjunct to valproate.

Weight loss can occur during topiramate *Verrotti et al (2011)* reviewed and quantified topiramate-induced weight loss, analyze the pathogenetic mechanisms and evaluate its clinical implications in patients with epilepsy. The amount of weight loss appears to be related to some factors such as the duration of the treatment and a high baseline body mass index (BMI), while the role of daily dosage and gender of patients is controversial. The mechanism through which topiramate may induce weight loss is still unclear. Topiramate is able to induce weight loss, especially in high baseline BMI patients, not strictly depending on daily dosage and perhaps not influenced by gender. This makes topiramate a good choice, especially in obese patients suffering from seizures. However, topiramate can make nutritionally vulnerable children or adult patients, with epilepsy associated with other neuropsychiatric diseases, who cannot voluntarily increase their caloric intake.

Dell'Orto et al (2013) systematically reviewed all the literature for association of topiramate with development of metabolic acidosis, hypokalaemia and renal stone disease. Fourty-seven reports published between 1996 and 2013 were retained for the final analysis. Five case–control studies and six longitudinal studies addressed the effect of topiramate on acid–base and potassium balance. A significant tendency towards mild-to-moderate hyperchloraemic metabolic acidosis (with bicarbonate ≤21.0 mmol/L in approximately every third case) and mild hypokalaemia (with potassium ≤3.5 mmol/L in 10% of the cases) was noted on treatment with topiramate, which was similar in children and adults. A single study observed that topiramate causes mild hyperuricaemia in male adults. A tendency towards hypocitraturia, a recognized promoter of renal stone formation, was noted in all patients on topiramate.

A study reviewed relationship between sexual function and topiramate (*Chen et al, 2017*). A total of 17 publications were reviewed. Based on limited polytherapy observational studies, the frequency of self-reported topiramate-associated SD, libido disorder, and orgasmic disorder in patients with polytherapy was 9.0%, 9.0%, and 2.6%, respectively (grade C evidence). Female patients mainly had

anorgasmia, whereas male patients principally had erectile dysfunction. Sexual adversity usually occurred from 4 weeks after topiramate use but favourably subsided without eventful complications after topiramate substitution or dose reduction in all patients.

Adverse effects according to organ systems:

(Post marketing reports of adverse drug reactions *(SPC, Topamax®, 2015):*

Infections and Infestations

Very common: nasopharyngitis

Blood and Lymphatic System Disorders

Common: anaemia

Uncommon: leucopenia and neutropenia, thrombocytopenia

Rare: neutropenia

Immune System Disorders

Common: hypersensitivity

Metabolism and Nutrition Disorders

Common: anorexia, decreased appetite

Uncommon: metabolic acidosis, hypokalaemia, increased appetite, polydipsia

Rare: acidosis hyperchloraemic

Psychiatric disorders

Very common: depression

Common: bradyphrenia, insomnia, expressive language disorder, anxiety, confusional state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behaviour

Uncommon: suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphemia, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood

Rare: mania, panic disorder, feeling of despair*, hypomania

Nervous system disorders

Very common: paraesthesia, somnolence, dizziness

Common: disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, tremor, lethargy, hypoaesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation

Uncommon: depressed level of consciousness, grand mal convulsion, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncope, sensory disturbance, drooling, hypersomnia, aphasia, repetitive speech, hypokinesia, dyskinesia, dizziness postural, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome, dysaesthesia, hypogeusia, stupor, clumsiness, aura, ageusia, dysgraphia, dysphasia, neuropathy peripheral, presyncope, dystonia, formication

Rare: apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli

Eye disorders

Common: vision blurred, diplopia, visual disturbance

Uncommon: visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia

Rare: blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception, scintillating scotoma, eyelid oedema*, night blindness, amblyopia

Not known: angle closure glaucoma*, maculopathy*, eye movement disorder* , conjunctival oedema*

Ear and labyrinth disorders

Common: vertigo, tinnitus, ear pain

Uncommon: deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired

Cardiac disorders

Uncommon: bradycardia, sinus bradycardia, palpitations

Vascular disorders

Uncommon: hypotension, orthostatic hypotension, flushing, hot flush

Rare: Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea , epistaxis, nasal congestion, rhinorrhoea, cough*

Uncommon: dyspnoea exertional, paranasal sinus hypersecretion, dysphonia

Gastrointestinal disorders

Very common: nausea, diarrhoea

Common: vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort

Uncommon: pancreatitis, flatulence, gastrooesophageal reflux disease, abdominal pain lower, hypoaesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia

Hepatobiliary disorders

Rare: hepatitis, hepatic failure

Skin and subcutaneous tissue disorders

Common: alopecia, rash, pruritus

Uncommon: anhidrosis, hypoaesthesia facial, urticaria, erythema, pruritus generalised, rash macular, skin discolouration, dermatitis allergic, swelling face

Rare: Stevens-Johnson syndrome* erythema multiforme*, skin odour abnormal, periorbital oedema*, urticaria localised

Not known: Toxic epidermal necrolysis*

Musculoskeletal and connective tissue disorders

Common: arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain

Uncommon: joint swelling*, musculoskeletal stiffness, flank pain, muscle fatigue

Rare: limb discomfort*

Renal and urinary disorders

Common: nephrolithiasis, pollakiuria, dysuria

Uncommon: calculus urinary, urinary incontinence, haematuria, incontinence, micturition urgency, renal colic, renal pain

Rare: calculus ureteric, renal tubular acidosis*

Reproductive system and breast disorders

Uncommon: erectile dysfunction, sexual dysfunction

General disorders and administration site conditions

Very common: fatigue

Common: pyrexia, asthenia, irritability, gait disturbance, feeling abnormal, malaise

Uncommon: hyperthermia, thirst, influenza like illness*, sluggishness, peripheral coldness, feeling drunk, feeling jittery

Rare: face oedema, calcinosis

Investigations

Very common: weight decreased

Common: weight increased*

Uncommon: crystal urine present, tandem gait test abnormal, white blood cell count decreased, Increase in liver enzymes

Rare: blood bicarbonate decreased

Social circumstances

Uncommon: learning disability

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* identified as an adverse reaction from postmarketing spontaneous reports. Its frequency was calculated based on clinical trial data.

Adverse reactions reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, hyperchloraemic acidosis, hypokalaemia, abnormal behaviour, aggression, apathy, initial insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, lacrimation increased, sinus bradycardia, feeling abnormal, gait disturbance.

Adverse reactions that were reported in children but not in adults in double-blind controlled studies include: eosinophilia, psychomotor hyperactivity, vertigo, vomiting, hyperthermia, pyrexia, learning disability.

Special Patient Groups

Children

In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated children were headache, anorexia and somnolence. Adverse events occurring at 5% or more but less than

10% included: difficulty with concentration/attention, fatigue, weight decrease, dizziness, paraesthesia, insomnia and nervousness.

Novotny et al (2010) evaluated the efficacy and safety of adjunctive topiramate (sprinkle capsules or oral liquid) in reducing daily rates of partial-onset seizures (POS) in infants with refractory POS. Treatment-emergent fever, diarrhoea, vomiting, anorexia, weight decrease, somnolence, and viral infection occurred more frequently (≥10% difference) with topiramate than with placebo.

The double-blinded, placebo-controlled CHAMP study compared the effectiveness of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine (*Powers et al, 2017*). The active drugs were associated with higher rates of adverse events (Table 4), paraesthesia (31% vs. 8%) and weight loss (8% vs. 0%) in the topiramate group.

Table 4. Adverse events and serious adverse events (after *Powers et al, 2017*)

Adverse Event	All Patients (N=361)	Amitriptyline (N=144)		Topiramate (N=145)		Placebo (N=72)	
	Adverse Events	Adverse Events	Serious Adverse Events	Adverse Events	Serious Adverse Events	Adverse Events	Serious Adverse Events
	number of patients (percent)						
Nervous system							
Aphasia	43 (12)	13 (9)	0	23 (16)	0	7 (10)	0
Cognitive disorder	45 (12)	14 (10)	0	23 (16)	0	8 (11)	0
Dizziness	13 (4)	3 (2)	0	9 (6)	0	1 (1)	0
Memory impairment	42 (12)	11 (8)	0	24 (17)	0	7 (10)	0
Paresthesia	61 (17)	10 (7)	0	45 (31)†	0	6 (8)	0
Syncope	3 (1)	3 (2)	1 (1)	0	0	0	0
General: fatigue	89 (25)	43 (30)†	0	36 (25)	0	10 (14)	0
Gastrointestinal							
Dry mouth	71 (20)	36 (25)†	0	26 (18)	0	9 (12)	0
Intussusception	1 (<0.5)	0	0	1 (1)	1 (1)	0	0
Infection							
Appendicitis	1 (<0.5)	0	0	0	0	1 (1)	1 (1)
Streptococcal pharyngitis	12 (3)	7 (5)	0	1 (1)†	0	4 (6)	1 (1)
Upper respiratory tract infection	42 (12)	14 (10)	0	18 (12)	0	10 (14)	0
Psychiatric							
Altered mood	29 (8)	11 (8)	3 (2)	14 (10)	0	4 (6)	0
Suicide attempt	1 (<0.5)	0	0	1 (1)	1 (1)	0	0
Investigations: decreased weight	11 (3)	0	0	11 (8)†	0	0	0
Injury, poisoning, or procedural complication							
Contusion	7 (2)	3 (2)	0	1 (1)	1 (1)	3 (4)	0
Hand fracture	3 (1)	0†	0	0†	0	3 (4)	0
Traumatic liver injury	1 (<0.5)	0	0	1 (1)	1 (1)	0	0
Respiratory: bronchospasm	5 (1)	3 (2)	1 (1)	1 (1)	0	1 (1)	0
Immune system: anaphylactic reaction	1 (<0.5)	1 (1)	1 (1)	0	0	0	0

Elderly

There were no differences in the frequency or intensity of AEs in elderly patients. In general, no dosage adjustments are required for geriatric patients. However, if the patient has experienced a decrease in glomerular filtration rate (GFR),

topiramate elimination will be affected. Close monitoring of clinical response and cautious modifications in dosage are appropriate in elderly patients *(Perucca & Bialer, 1996).*

Ramsay et al (2008) compared two dosages of topiramate in a pilot study of patients ≥60 years of age with partial-onset seizures. In this 24-week, double-blind, randomized, parallel-group study, patients with one or more seizures in previous 6 months were randomized to treatment with 50 or 200 mg/day topiramate. Topiramate was initiated as monotherapy or added to one AED and titrated by 25 mg/day per week to target or maximum tolerated dose as the concomitant AED, if any, was withdrawn. Thirty-eight patients were randomized to the 50 mg/day topiramate (mean age, 68 years) and 39–200 mg/day topiramate (69 years). The overall incidence of adverse events was similar for the two dosages—66% with 50 mg and 62% with 200 mg topiramate. Most common adverse events were somnolence (topiramate 50, 13%; topiramate 200, 8%), dizziness (13% vs. 8%), and headache (13% vs. 5%).Of 10 (13%) patients reporting a cognitive-related adverse event, six patients were assigned to the 50-mg group. A total of 14 patients (18%; seven in each group) discontinued topiramate due to adverse events. This pilot study supports the practice of using low-to-moderate dosages of AEDs in older adults.

Sommer and Fenn (2010) reviewed topiramate efficacy and pharmacokinetics with emphasis on the older patient, and adverse events in both the younger and older adult. Even in studies of younger individuals, up to 50% discontinued topiramate because of intolerable cognitive deficits. Most studies found specific declines in working memory and verbal fluency. They recommend to begin topiramate slowly, maintain the patient at the lowest possible dose, below 200 mg if possible, and to monitor the patient for amelioration of cognition over several months.

Pregnancy and Breast Feeding

Teratology studies demonstrated that topiramate is teratogenic in mice, rats, and rabbits. In mice festal weights and skeletal ossification were reduced by topiramate at 500 mg/kg/day in conjunction with maternal toxicity. In rats, limb and digit defects were noted at 400 mg/kg/day and higher doses. In rabbits, rib and vertebral malformations occurred at 120 mg/kg/day. The teratogenic effects observed in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans.

Use of certain antiepileptic drugs during pregnancy increases the risk for specific congenital malformations. In a study, the risk for congenital malformations was compared in offspring between women with epilepsy being treated with antiepileptic drugs during pregnancy and those who discontinued their antiepileptic medication before pregnancy in a population-based cohort of female patients with epilepsy. Methods: All patients with epilepsy (n = 20,101) eligible for antiepileptic drug reimbursement for the first time during 1985 to 1994 were identified from the Social Insurance Institution of Finland. Information on births during 1991 to 2000 was obtained from the National Medical Birth Registry. Information on antiepileptic drug use during pregnancy and on pregnancy outcomes was abstracted from medical records. Congenital malformations were more common among offspring of women on antiepileptic medication (65/1,411; 4.6%) than among offspring of untreated patients (26/939; 2.8%) (p <0.02).

Excess risk was confined to patients using valproate during pregnancy. The risk for malformations was not elevated in offspring of mothers using carbamazepine, oxcarbazepine, or phenytoin (as monotherapy or polytherapy without valproate) *(Artama et al, 2005)*.

There were 28 cases of topiramate exposure in the UK Epilepsy and Pregnancy Register, 2 of which resulted in children with major malformations *(Morrow et al, 2006)*. The small number of exposures does not permit conclusions on whether there is an increase in risk. It is possible that the background risk of malformations is increased in the offspring of women with seizure disorders, irrespective of the medication used to treat the seizure disorders. Anticonvulsant medications for which there is human pregnancy experience appear to increase the incidence of malformations as well. Although there are no large scale prospective studies on the use of topiramate in human pregnancy, the experimental animal response and case report are consistent with the toxicity potential of other anticonvulsant medications.

An additional clinical study involving five women who took topiramate during gestation has demonstrated the transplacental passage of this agent and its excretion in milk *(Öhman et al, 2002)*. The umbilical cord plasma/maternal plasma ratios in all of these five deliveries were close to unity, suggesting ready transplacental transfer of topiramate. The mean milk/maternal plasma concentration ratio was 0.86 (range, 0.67-1.1) 2-3 weeks after delivery. The milk/maternal plasma concentration ratios 1 and 3 months after delivery were similar (0.86 and 0.69, respectively). Two to three weeks after delivery, 2 of the breast-fed infants had detectable (>0.9 µM) concentrations of topiramate, although below the limit of quantification (2.8 µM),and one had an undetectable concentration. Breast-fed infants had very low topiramate concentrations, and no adverse effects were observed in the infants.

Gorman & Soul (2007) described two siblings with neonatal hypocalcaemic seizures whose mother took topiramate during both pregnancies. Apart from hypocalcaemia, the patients had no identifiable aetiology for their seizures. Although biochemical data suggested that the hypocalcaemia was caused by hypoparathyroidism, no disorders typically associated with this condition were identified in the patients. The authors propose that topiramate exposure in utero led to hypoparathyroidism and subsequent hypocalcaemia via effects on protein kinase A signaling, resulting in hypokalaemic seizures. Neonates exposed to topiramate in utero should be monitored for hypokalaemic seizures.

Castilla-Puentes et al (2014) evaluated foetal or neonatal outcomes (with a focus on major congenital anomalies) with use of topiramate monotherapy and examined whether differences occurred in the reporting and patterns of these outcomes for pregnant women with and without epilepsy. Spontaneous, postmarketing reports involving women who used topiramate monotherapy during pregnancy from 18 July 1995 (International Birth Date of topiramate) through 30 April2011 were retrieved from the sponsor's (Janssen Research & Development, LLC) Global Medical Safety database. All formulations for topiramate, used as monotherapy, were selected for the analysis. Monotherapy was defined as any situation where no other AED was listed in the pregnancy case report, either as a suspect or concomitant medication, regardless of indication. A total of 1163 cases of women who used topiramate monotherapy during pregnancy (for any indication) were retrieved from the Global Medical Safety database. Since some

women used topiramate for more than one indication, there were a total of 1199 reported indications for topiramate monotherapy, which were primarily for treatment of epilepsy (n = 599), accounting for half of the indications, and migraine prophylaxis (n = 240, 20.0%). Out of 1163 cases, pregnancy outcome was reported in 50.6% (n = 589). Live birth was the most frequently reported outcome, regardless of indication (epilepsy, 78.8% [312/396]; prophylaxis of migraine,59. 3% [48/81]; other indication, 64.4% [85/132]). Cleft lip or palate anomalies (epilepsy, n = 15; migraine, n = 2; other indication, n = 4; and indication not reported, n = 2), limb, hand, or other skeletal anomalies (epilepsy, n = 13; migraine, n = 2; other indication, n = 0; and indication not reported, n = 1), and respiratory or cardiovascular anomalies (epilepsy, n = 12; migraine, n = 1; other indication, n = 1; and indication not reported, n = 2) were the most often reported major foetal or neonatal anomalies. More reported major foetal or neonatal anomalies occurred in patients being treated for epilepsy (53/79 anomaly-indication pairs) compared with patients being treated for migraine prophylaxis (10/79 anomaly-indication pairs). Although incidence rates cannot be calculated based on spontaneous adverse event reporting, this summary of reported pregnancy and neonatal outcomes with use of topiramate monotherapy suggests that the risk for major foetal or neonatal anomalies may differ based on the indication for topiramate.

Alsaad et al (2015) conducted a meta-analysis of all studies reporting on women exposed to topiramate during pregnancy. Of the 2327 publications reviewed, 6 articles met the inclusion criteria including 3420 patients and 1,204,981 controls. The odd ratio (OR) of oral cleft (OC) after the first trimester exposure to topiramate exposure was 6.26 (95% CI: 3.13–12.51; P = 0.00001). This study provides strong evidence that topiramate is associated with an increased risk of OC in infants exposed to topiramate during embryogenesis and should lead to a careful review of topiramate use in women of reproductive ages.

Overdosage

Overdoses of topiramate have been reported *(Smith et al, 2001; Fakhoury et al, 2002, Langman et al, 2003)*. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mental impairment, lethargy, metabolic acidosis, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have also been reported (*Langman et al, 2003*). *Smith et al (2001)* reviewed the medical records of two patients who took a topiramate overdose as a suicide attempt. They recorded their medical and seizure histories, concomitant antiepileptic medications, neurologic examination, and laboratory findings at the time of presentation following the overdose. Their progress and the evolution of laboratory abnormalities were also recorded. Both patients progressed to coma and had generalized convulsive status epilepticus, requiring intubation and treatment with benzodiazepines. Both patients recovered within 2 days but had a non-anion-gap metabolic acidosis that persisted for 5–6 days. *Fakhoury et al (2002)* reported the case of a 24-year old woman who ingested 4000 mg of topiramate in a suicide attempt. She was asymptomatic following the overdose and did not develop any adverse sequelae. In this article they discussed the commonly seen side effects of topiramate use and examined the available data concerning topiramate overdose.

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. Haemodialysis is an effective means of removing topiramate from the body.

Summary of Clinical Safety

In controlled trials of topiramate as adjunctive therapy, the most commonly reported AEs included dizziness, slowed thinking, somnolence, ataxia, fatigue, confusion, impaired concentration and paraesthesia. The incidence of AEs was highest during the initial 2 months corresponding to the titration period. Many adverse events resolved with continued topiramate treatment. AEs associated with carbonic anhydrase inhibition, that is paraesthesia and nephrolithiasis, have been reported with topiramate. Renal calculi occurred in 1.5% of patients given topiramate. Patients receiving topiramate should be encouraged to maintain adequate hydration. Body weight decreases were reported; the greatest mean bodyweight losses were reported for patients in the highest weight ranges. Topiramate is well tolerated in children.

The addition of topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in some patients where the addition of topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of the latter. Less important interactions with other drugs may occur, in particular with CNS depressants, digoxin, oral contraceptives, lithium, hydrochlorothiazide and antidiabetic drugs.

2.5.6. Benefits and Risks Conclusions

Topiramate is a sulphamate-substituted monosaccharide derived from D-fructose and structurally unrelated to other antiepileptic drugs. It acts by multiple mechanisms, suggesting that it may be effective in multiple type of epilepsy.

Topiramate is readily absorbed after oral doses, with peak plasma concentrations achieved after about 2 hours. Bioavailability is not affected by the presence of food. Protein binding is about 9 to 17%. The volume of distribution in women is about half that in men. Topiramate crosses the placental barrier and is distributed into breast milk. In healthy subjects topiramate is not extensively metabolised; however, up to 50% of a dose may undergo metabolism in the liver in patients also receiving enzyme-inducing drugs. It is eliminated chiefly in urine, as unchanged drug and metabolites; mean plasma elimination half-life is about 21 hours. Steady-state concentrations are achieved after about 4 to 8 days in patients with normal renal function. Clearance is decreased in patients with impaired renal or hepatic function, and steady-state plasma concentrations may not be achieved for 10 to 15 days in the former. Children exhibit a higher clearance and shorter elimination half-life than adults. The pharmacokinetics of topiramate may be affected by use with other antiepileptics.

The effectiveness of topiramate as an adjunctive treatment for adults with partial onset seizures was established in multicentre, randomized, double-blind, placebo-controlled studies, as well as for paediatric patients ages 2-16 years with partial onset seizures. The effectiveness of topiramate as an adjunctive treatment for primary generalized tonic-clonic seizures in patients 2 years old and older was established multicenter, randomized, double-blind, placebo-controlled trial, comparing a single dosage of topiramate and placebo. The effectiveness of topiramate as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome was also established in a multicenter, randomized, double-blind, placebo-controlled trial comparing a single dosage of topiramate with placebo in patients 2 years of age and older. In several controlled trials the efficacy and safety of topiramate was also assessed for migraine prevention.

Topiramate is indicated as monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures; as an 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. Topiramate is also indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute

For both adjunctive and monotherapy of epilepsy, the initial dose of topiramate in adults is 25 mg once daily by mouth for one week increased thereafter by increments of 25 to 50 mg at intervals of one to two weeks until the effective dose is reached. Daily doses of more than 25 mg should be taken in 2 divided doses. The usual daily dose for adjunctive therapy is 200 to 400 mg although some patients may require up to 800 mg daily. When used as monotherapy, usual doses range from 100 mg daily to a maximum of 400 mg daily. Similar target doses are also used in the USA for both adjunctive and monotherapy although higher initial doses of 50 mg daily with weekly increases thereafter are

recommended in the licensed drug information. The initial dose as adjunctive therapy for children aged 2 to 16 years is 25 mg nightly for the first week, increased at intervals of one to two weeks by increments of 1 to 3 mg/kg daily, according to response. The recommended dose thereafter is about 5 to 9 mg/kg daily given in 2 divided doses, although up to 30 mg/kg daily has been given. For monotherapy, children aged 6 years and over may be started on 0.5 to 1 mg/kg at night for the first week, increased at intervals of one to two weeks by increments of 0.5 to 1 mg/kg daily. The usual dose is 3 to 6 mg/kg daily in 2 divided doses, although higher doses have been tolerated. In the USA, the use of topiramate as monotherapy is limited to those children aged 10 years and over; doses are similar to those used in adults (see above).

In the prophylaxis of migraine in adults, topiramate is given in initial doses of 25 mg daily, increased by 25-mg increments every week, to a usual dose of 50 mg twice daily by mouth.

Smaller increments or longer intervals between increments may be necessary if patients cannot tolerate the above regimen; doses should be reduced in patients with moderate to severe renal impairment.

As with other antiepileptics, withdrawal of topiramate therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures.

In patients with impaired renal and/or hepatic function lower doses are recommended, caution should be exercised. No dose adjustment is required in the elderly.

Topiramate is contraindicated in hypersensitivity to the active substance or to any of the excipients. Topiramate is also contraindicated for migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

Adverse effects associated with topiramate therapy include ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia or hypoaesthesia, drowsiness, and difficulties with memory or cognition. Agitation, anxiety, nervousness, emotional lability (with mood disorders), and depression may also occur. Other reported adverse effects include abdominal pain, anorexia, asthenia, diplopia, leucopenia, nausea, nystagmus, insomnia, psychomotor retardation, impaired speech, altered taste, visual disturbances, and weight loss. The risk of developing renal calculi is increased, especially in predisposed patients. Reduced sweating with hyperthermia has occurred particularly in children. Rare cases of acute myopia with secondary angle-closure glaucoma have been reported.

The addition of topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in some patients where the addition of topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of the latter. Less important interactions with other drugs may occur, in particular with CNS

depressants, digoxin, oral contraceptives, lithium, hydrochlorothiazide and antidiabetic drugs.

Topiramate Rosemont 10 mg/ml and 20 mg/ml Oral Suspension has been shown to be bioequivalent to the brand leader Topamax® and is intended for the same indications in the same dosages as this product.

In conclusion, topiramate is a safe and effective antiepileptic drug with well established use for the treatment of various forms of epilepsy as well as for prophylaxis of migraine. If used appropriately (according to the SPC) it is fairly safe. Practical experience of topiramate on the market in a large number of patients has also confirmed its safety and efficacy. These facts provide sufficient support for its use.

2.5.7. Literature References

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