International Journal of Clinical Pharmacology and Therapeutics, Vol. 48 – No. 5/2010 (342-348)

Original

ISSN 0946-1965

Relative bioavailability study with two oral formulations of topiramate using a validated UPLC-MS/MS method

I. Saavedra[1], E. Tamayo[1], A. Gamboa[1], J. Sasso[1], N. Varela[1], I. Moreno[1], D. Marchant[1], D. Cáceres[2] and L. Quiñones[1]

[1]Laboratory of Pharmacokinetics and Bioavailability, IFT, Molecular and Clinical Pharmacology Program, Biomedical Sciences Institute, Faculty of Medicine, University of Chile, and [2]Epidemiology Division, School of Public Health, Faculty of Medicine, University of Chile, Santiago, Chile

Key words
bioavailability – pharmacokinetics – bioequivalence – topiramate

Abstract. Changes in bioavailability of anticonvulsant drugs such as topiramate may cause loss of or worsened seizure control. Thus, the purpose of this study was to evaluate, in a double-blind crossover design, the bioavailability between two oral formulations of topiramate in healthy volunteers after a single dose. The protocol, approved by the Institutional Committee of Ethics, consisted of administration of 1 tablet of 100 mg of topiramate of each formulation (Toprel™ and Topamax™), to 20 healthy volunteers after a 12 h overnight fast, using an open, two-period, randomized, crossover and double-blind design. Thus, the plasma concentrations (Cp) of topiramate were measured at predetermined intervals of time, from 0 to 24 h, using a validated UPLC-MS/MS method. Based on plasma concentration-time profiles we obtained the following pharmacokinetic parameters: $AUC_{0-\infty}$ 63,418.31 ± 22,141.69 and 67,094.70 ± 22,487.2 ngh/ml; AUC_{0-24}: 30,421.02 ± 9,964.0 and 30,489.35 ± 9,407.17, ng × h/ml; t_{max}: 2.77 ± 1.76 and 1.95 ± 1.89 h; C_{max}: 2,143.33 ± 724.26 and 2,262.51 ± 751.12 ng/ml, for A (Toprel™) and B (Topamax™), respectively. All these differences were not statically significant with 90% confidence interval. The test of bioequivalence showed that C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ parameters are found within the range of 0.8 – 1.25 recommended by the FDA with a probability of bioequivalence of 100%. In accordance with these results, we can conclude that Toprel™ 100 mg, A (Test), is a bioequivalent generic and interchangeable with Topamax™ 100 mg, B (Reference).

Received
January 30, 2009;
accepted
September 9, 2009

Correspondence to
L.A. Quiñones,
Biochemist
IFT, Molecular and
Clinical Pharmacology
Program, Biomedical
Sciences Institute,
Faculty of Medicine,
University of Chile,
PO Box 70111,
Santiago 7, Chile
lquinone@
med.uchile.cl

Introduction

Topiramate (TPM) is a sulfamate-substituted monosaccharide (2,3:4,5-bis-O-(1-methyliden)-β-D-fructopiranose sulfamate) with antiepileptic (AED) properties. This drug has been approved in about one hundred countries as adjunctive therapy for the treatment of partial and primary generalized tonic-clonic seizures and migraine prophylaxis in adult [1] and is simpler to use than traditional AEDs due to favorable pharmacokinetic characteristics and fewer drug and food interactions [13, 18, 23, 27].

Three mechanisms contributing to pharmacological activity of topiramate have been described including modulation of voltage-dependent sodium channels, potentiation of gabaergic inhibition and blockage of a subtype of glutamate receptors [22]. Its intrinsic inhibiting activity of carbonic anhydrase does not contributes to antiepileptic action [15].

The pharmacokinetic of TPM is characterized by linearity in a wide range of doses [27]. The drug is quickly absorbed having poor plasma protein binding. It has a long half-life and the maximum concentration is reached 2 – 4 h after dose which is not affected by food consumption or sex differences [4, 5, 15]. A bioavailability of about 81 – 95% for 100 mg – 1,200 mg/day in healthy volunteers has been described [3, 27].

TPM is metabolized at a rate of about 8 – 9% and is excreted unalteredly by 59%. The main metabolite in urine is the glucuronide derivative. This situation changes dramatically in concomitant phenytoin, carbamazepine or phenobarbital treatments, by age or in reduced kidney function as has been shown by previous studies with enzyme-inducing anticonvulsants (i.e., phenytoin, carbamazepine),

and age. Children need a higher dose to achieve the same drug levels than adults, and adjustments are required in co-medication with enzyme-inducing AEDs due to their inducing metabolization of TPM [2, 10, 20].

Six clinical trials, placebo-controlled, double-blind studies have shown that TPM is well tolerated and effective as coadjuvant therapy for partial epileptic crisis in adults [11, 26]. Several other published studies have shown safety and efficacy of TPM as adjuvant in schizophrenia and migraine or monotherapy in partial epileptic crisis of children with Lennox-Gastaut syndrome and also in patients with tonic-clonic crisis suggesting a wide spectrum of clinical use for TPM [6, 14, 19].

There are factors that may cause therapeutic failures in the treatment of epileptic seizures, including patient's non-compliance, type of epilepsy and multisource pharmaceutical products. Thus, bioequivalence (BE) or relative bioavailability (BA) studies are performed to show that two products (generic and innovator) containing the same active substance are clinically equivalent and interchangeable, without a significant change on the steady-state plasma concentration, associated with drug [7, 24]. However, due to variability generic drugs can be highly problematic for patients with epilepsy, special caution may be needed for patients at highest risk of seizure complications [17].

This study was conducted to assess the bioavailability of a 100 mg topiramate oral formulation, compared to the bioavailability of 100 mg topiramate innovating formulation, according to the FDA and EMEA recommendations to assess the bioequivalence.

Methods

The following products were employed in this study: Toprel™ 100 mg film-coated tablets, from Drugtech-Recalcine Laboratories S.A (Santiago, Chile) as the test formulation and Topamax™ film-coated tablets, from Janssen-Cilag (Baar, Switzerland) as the reference formulation.

The researchers were blind to the assayed products (A or B) and these were tested by using physicochemical test (data not shown).

The formulations were administered by using a blind, randomized, crossover and comparative experimental design. 20 volunteers were divided in two groups. The first group received an oral dose of 100 mg tablet of the Product A (Toprel™) and second group of Product B (Topamax™). 1 week was elapsed between treatment periods. Thus, each group was crossed over to receive the other product in the second period.

Formulations were administered to volunteers after a 12-h overnight fast with 250 ml drinking water and under medical supervision. Blood samples were obtained in heparinized polypropylene tubes before dosing and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12 and 24 h. After centrifugation, plasma samples were stored in plastic tubes at –20 °C until assayed.

Topiramate concentrations were determined by using the LC-MS/MS method described by Park et al. [16], with some modifications. The system consisted of an ACQUITY™ UPLC (Ultra Performance Liquid Chromatograph) and a Micromass Quattro triple quadruple spectrometry detector from Waters [16]. The chromatography column was bridged ethylene hybrid (BEH) C_{18} 100 × 2.1 mm 1.7 µm and the mobile phase methanol: ammonia acetate 10 mM (pH 6.3) in proportion 90 : 10, respectively. The detector was operated in the negative ionization and the multiple reaction monitoring (MRM) transitions monitored were m/z 338.0→77.0 and m/z 407→185.0 for topiramate and internal standard (tamsulosin). The samples (200 µl of plasma) with 50 µl Internal standard and 50 µl HCl (0.1 N) were extracted with 4 ml ethyl acetate. These were well agitated with automatic shaker, followed by centrifugation at 3,600 × g for 10 min. Thus, 2 ml of the organic layer was extracted of each sample and evaporated to dryness under a stream of nitrogen in an evaporator. The residue was reconstituted with 200 µl of mobile phase and transferred into glass injection vials for analysis. Quality control samples were prepared to contain 1.0, 2.5, 5.0 and 7.5 µg/ml and incorporated into each analytical run.

Plasma concentrations of topiramate were plotted lineally and logarithmically. Thus, concentration-time average profiles were constructed for Product A (Toprel™) and Product B (Topamax™). The maximum plasma concentration (C_{max}) and time to reach the maximum concentration (t_{max}) were deter-

mined by direct inspection of the curves. Other pharmacokinetic parameters such as the elimination rate constant (K_e), half-life ($t_{1/2}$), area under the plasma concentration-time curve AUC_{0-t} and $AUC_{0-\infty}$ were calculated by using pKexamine from STATA 10.0 software. AUC-RPP software for independent compartment model was employed as a comparative model and additional pharmacokinetics parameters were obtained, such as apparent volume (V_d) and clereance (Cl).

FDA requirements were adopted for demonstrating bioequivalence between both formulations. These stipulate that 90% confidence intervals for the ratio of the parameter averages (AUC and C_{max}) should fall within the standard criteria of 80 – 125%.

An analysis of variance (ANOVA) was employed to establish the significant differences between the parameters of each formulation. Values of $p < 0.05$ were considered as significant. FDA recommendations were adopted for the design of the study and pharmacokinetic and statistical analysis. The formulation, period of administration, sequence and residual effects were considered as source of variations. Thus, the 90% confidence intervals were calculated for average differences obtained with Product A (Toprel™) and Product B (Topamax™). STATA v 10.0 and Schuirmann's two one-sided tests were used for it [21].

The research was approved by the Institutional Committee of Ethics and the procedures employed were according to the declaration of Helsinki and Good Clinical Practices of FDA [12].

Materials

Standards, chemicals and HPLC grade water and solvents were purchased from Merck (Darmstadt, Germany). Chromatography column BEH C_{18} and vials for UPLC system were from Waters Corp. (Milford, MA, USA).

Subjects

30 adult volunteers, including Hispanic Americans, males and females, ranging in age from 18 to 55 years were enrolled. All subjects were evaluated by medical history and clinical chemistry test, blood analysis, glycemia, HIV, pregnancy test and urinalysis and 24 healthy volunteers were selected who provided written informed consent to participate in the study after receiving details of the study's purpose. Reasons for exclusion included: any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs; a history of clinically significant problems including gastrointestinal, renal, endocrine, hepatic, dermatologic, hematologic, immunologic, psychiatric or neurologic disorders; drug hypersensitivity, alcoholism or drug abuse; having participated in a similar study within the previous 3 months, eventually pregnant, lactating, having presented any significant sickness within the previous 30 days, having used any drug within the previous 7 days, including OTC drugs, HIV positive, having a history of fainting and blood-injury phobia.

Results

24 healthy volunteers were selected for the study and only 20 completed it. Two persons did not arrive at the research center, 1 person had problems with blood extraction and 1 person observed nausea and dizziness during the second period, therefore he was excluded from the study.

Table 1 provides the anthropometric and biochemical characteristics and the identification of the 20 volunteers finally included in this study. Mean age of the group was 28.5 years (range 20 – 53); mean body weight was 69.9 kg (range 49.5 – 100.5); Mean body height was 166.2 cm (range 149 – 180) and mean body mass index was 25.2 kg/m^2 (range 19.8 – 31.0). The values for glycemia, ureic nitrogen, urea, creatinine, bilirubin, alkaline phosphatase, AST, ALT and total protein ranged within normal values for all volunteers, supporting their healthy conditions.

A new UPLC-MS/MS method was employed in this study which was validated from 0.1µg/ml LLOQ to 7.5 µg/ml ULOQ. The signal to noise at 0.1 µg/ml was 70. Assay accuracy, measured as relative error ranged from –2.58 to 3.72% and assay precision

Table 1. Baseline characteristics of subjects.

Characteristics	Value ± SD (n = 20)
Demographic	
Age (mean ± SD)	28.5 ± 9.94
Weight	69.99 ± 11.77
Height	166.25 ± 9.23
Body mass index (BMI)	25.24 ± 3.05
Sex (male/female)	10/10
Biochemical	
Glycemia (60 – 100 mg/dl)	84.67 ± 8.98
Ureic nitrogen (6 – 20 mg/dl)	13.45 ± 2.78
Urea (10 – 50 mg/dl)	27.94 ± 6.54
Creatinine (0.8 – 1.5 mg/dl)	0.85 ± 0.16
Bilirubin (0.2 – 1.3 mg/dl)	0.66 ± 0.25
Alkaline phosphatase (35 – 129 IU/l)	77.11 ± 17.05
AST (5 – 40 IU/l)	25.16 ± 5.94
ALT (7 – 56 IU/l)	24.16 ± 9.46
Total protein (6.6 – 8.7 g/dl)	7.79 ± 0.58

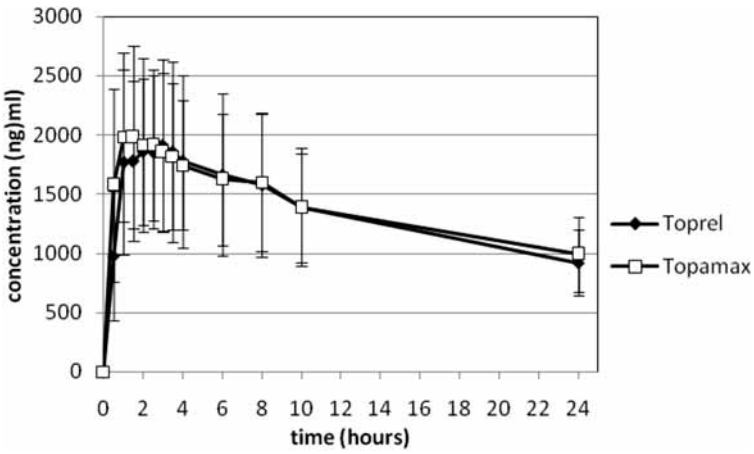

Figure 1. Mean plasma concentration-time profiles of topiramate.

measured as CV was < 3.46%. The standard curves exhibited good linearity ($R^2 > 0.999$) and chromatographic run was 1.5 minutes.

Figure 1 illustrates the mean plasma concentration-time profiles (± SD) of topiramate and Table 2 shows main pharmacokinetic parameters obtained for both formulations. There were no significant differences in C_{max}, $AUC_{0–t(24)}$ and $AUC_{0–\infty}$. p-value = 0.02 obtained for t_{max} indicates a significant difference, however this parameter is not used to establish bioequivalence for this drug.

Both formulations presented similar pharmacokinetic profiles and mean C_{max} values were 2,143.3 ± 724.3 ng/ml and 2,262.5 ± 751.1 ng/ml; 7.62 ± 0.31 and 7.68 ± 0.33 as logarithmic for Test and Reference, resptively. Areas under the plasma concentration-time curve $AUC_{0–t(24)}$ were 3,0421 ± 9,964 ng × h/ml and 30,489 ± 9,964 ng × h/ml; 10.27 ± 0.32 and 10.28 ± 0.30 as logarithmic for Test and Reference, respectively. Values of $AUC_{0–\infty}$ were 63,418 ± 22,141 ng × h/ml and 65,285 ± 21,670 ng × h/ml/ml; 10.99 ± 0.36 and 11.04 ± 0.33 as logarithmic for Test and Reference, respectively.

The elimination rate constant (K_e) was 0.033 + 0.02 for Toprel™ and 0.0293 ± 0.01 for Topamax™, the elimination half-life ($t_{1/2}$) was 25.22 ± 10.22 h for Toprel™ and 26.10 ± 9.58 for Topamax™, the distribution volume (V_d) was 0.83 ± 0.22 for Toprel™ and 0.82 ± 0.19 for Topamax™ and the clearence (Cl tot/f) was 0.43 ± 0.15 for Toprel™ and 0.41 ± 0.13 for Topamax™ (Table 2).

Statistical tests are shown in Table 3 using logarithmic transformed data according to FDA (2001b). 90% confidence intervals for the Test/Reference ratio were 97.76 – 100.15%, 98.39 – 100.43% and 98.25 – 101.17% for C_{max}, $AUC_{0–t}$ (24) and $AUC_{0–\infty}$. Moreover, the probability of exceeding the limits of acceptance (Schuirmann's two one-sided test) and the p-value for the probability of bioequivalence are also shown.

Discussion

The FDA and WHO designates a generic drug as therapeutically equivalent to the reference compound (usually the brand-name drug) if it contains an identical amount of active ingredient in the same dosage form and meets the equivalent standards for strength, quality, purity and identity [9, 25]. This is particularly relevant for psychotropic drugs such as anticonvulsants due to their variability [17]. Therefore, we conduct a bioequivalence study according to the FDA recommendations and using a high quality method by UPLC-MS/MS which have been validated also according to the FDA recommendations [8].

Table 2. Mean pharmacokinetics parameters after single dose of topiramate.

	C_{max} (ng/ml)	t_{max} (h)	Elimination rate	Half-life (h)	AUC_{0-24} (ng × h/ml)	$AUC_{0-\infty}$ (ng × h/ml)	Vd (l/kg)	Cl tot/f (ml/min/kg)
Toprel™								
Mean	2,143.33	2.78	0.0332	24.55	30,421.02	63,418.31	0.83	0.43
SD	724.26	1.77	0.02	9.58	9,964.01	22,141.69	0.22	0.15
CV %	33.79	63.6	47.50	39.02	32.75	34.91	27.00	34.78
Maximum	3,960.93	8.00	0.08	44.97	53,033.11	107,000.00	1.12	0.72
Minimum	1,211.00	1.00	0.02	8.17	18,166.39	33,778.52	0.43	0.22
Median	1,919.87	2.00	0.03	23.21	29,936.77	67,900.67	0.89	0.38
Topamax™								
Mean	2,301.55	1.95	0.0302	24.54	30,729.16	65,285.62	0.82	0.41
SD	762.70	1.90	0.01	7.13	9,240.23	21,670.33	0.19	0.13
CV %	33.14	97.34	24.12	29.05	30.07	33.19	23.22	30.9
Maximum	4,217.23	8.00	0.04	40.96	51,823.42	108,000.00	1.15	0.71
Minimum	1,118.51	0.50	0.02	16.39	13,900.83	29,608.12	0.50	0.19
Median	2,352.85	1.25	0.03	22.48	29,906.13	57,965.77	0.83	0.41

Table 3. Bioequivalence test.

	Classic bioequivalence intervals					Schuirmann's test		
	Equivalence limits		Limits test		Bioequivalence probability (%)	Two one-side tests		p-value
	Topamax™ vs. Toprel™							
LnC_{max}								
difference	–1.539	1.539	–0.172	0.012	100.00	Upper side	–30.612	< 0.0001
ratio	80%	125%	97.76%	100.15%		Lower side	27.579	< 0.0001
$LnAUC_{0-t}$								
difference	–2.062	2.062	–0.166	0.045	100.00	Upper side	–34.960	< 0.0001
ratio	80%	125%	98.39%	100.43%		Lower side	32.975	< 0.0001
$LnAUC_{0-\infty}$								
difference	–2.206	2.206	–0.192	0.129	100.00	Upper side	–24.121	< 0.0001
ratio	80%	125%	98.25%	101.17%		Lower side	23.441	< 0.0001

In Figure 1 and Table 2 we can observe a very similar pharmacokinetic behavior for both formulations. Differences between C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ which are the parameters for establishment of bioequivalence are not statistically significant. This issue shows that, in terms of extent of absorption of the drug, both formulations were similar. Same behavior was statistically observed for elimination rate, half-life and t_{max} (data not shown).

Table 3 shows that the ranges for the ln-transformed values of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are within the FDA criteria of 80 – 125%. On the other hand, Schuirmann's test indicated similar results with $p < 0.0001$ for tested hypotheses.

This bioequivalence study like any other clinical trial has some limitations to consider. Because the data were obtained from healthy Caucasians Chilean subjects who received a

single dose of topiramate, the pharmacokinetic characteristic should differ from patients and from other non Caucasian populations. However, this is a very good reference for similar Latino American populations.

Conclusion

Plasma concentrations of topiramate as well as other anticonvulsants can be affected by several factors including multisource pharmaceutical products. This study using a sensitive, specific and high-throughput UPLC/MS-MS method demonstrated that in pharmacokinetic parameters such as C_{max}, $AUC_{0-t(24)}$ and $AUC_{0-\infty}$, there were no statistically significant differences for two topiramate formulations. Based on these results and on FDA criteria, Toprel™ 100 mg, Drugtech Recalcine Laboratories S.A (Test product), is bioequivalent and interchangeable with Topamax™, Janssen-Cilag (Reference product).

Acknowledgment

The authors wish to thank Mrs. Magdalena Orellana, Ms. Jeannette Hermosilla, Ms. Paula Santander, Mr. Héctor Valenzuela, Mr. Ramiro Pérez, Mr. Santiago Leyton and Mr. Juan Rojas for their excellent technical support and also Biohealth LLC Clinical Research for its collaboration.

References

[1] *Bialer M, Doose DR, Murthy B, Curtin C, Wang SS, Twyman RE, Schwabe S.* Pharmacokinetic interactions of topiramate. Clin Pharmacokinet. 2004; *43:* 763-780.

[2] *Britzi M, Perucca E, Soback S, Levy RH, Fattore C, Crema F, Gatti G, Doose DR, Maryanoff BE, Bialer M.* Pharmacokinetic and metabolic investigation of topiramate disposition in healthy subjects in the absence and in the presence of enzyme induction by carbamazepine. Epilepsia. 2005; *46:* 378-384.

[3] *Doose D, Gisclon L, Stellar S et al.* The effect of food on the bioavailability of topiramate from 100-and 400-mg tablets in healthy male subjects. Epilepsia. 1992; *33:* 105.

[4] *Doose D, Scott VV, Margul B et al.* Multiple-dose pharmacokinetics of topiramate in healthy male subjects. Epilepsia. 1988; *29:* 662.

[5] *Easterling D, Zakszewski T, Meyer MD et al.* Plasma pharmacokinetics of topiramate, a new anticonvulsant in humans. Epilepsia. 1988; *29:* 662.

[6] *Faught E, Wilder BJ, Ramsay RE, Reife RA, Kramer LD, Pledger GW, Karim RM.* Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD Study Group. Neurology. 1996; *46:* 1684-1690.

[7] *FDA.* Guidance for Industry. "E6 Good Clinical Practice: consolidate guidance" US. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research; April 1996.

[8] *FDA.* Guidance for Industry. Bioanalytical Method Validation. U.S. Department of Health and Human Services. Food and Drug Administration. In CfVMC Center for Drug Evaluation and Research (CDER); May 2001.

[9] *FDA.* Guidance for Industry Statistical Approaches to Establishing Bioequivalence U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); January 2001.

[10] *Gisclon L, Curtin C, Kramer L.* The steady-state (SS) pharmacokinetics (PK) of phenytoin (Dilantinm) and topiramate (Topamax® in epileptic patients on monotherapy, and during combination therapy. Epilepsia. 1994; *35:* 54.

[11] *Glauser TA.* Topiramate. Epilepsia. 1999; *40 (Suppl):* 71-80.

[12] *Helsinki.* Declaración de Helsinki. Recomendaciones para guiar a los médicos en la investigación biomédica en seres humanos, hecha por la Asociación Médica Mundial en la Asamblea del Helsinki, Finlandia, en 1964. In: Ética Médica normas y documentos. Colegio Médico de Chile AG. Graphos Comunicaciones Ltda; 1986. pp. 91-95.

[13] *Lyseng-Williamson KA, Yang LP.* Topiramate: a review of its use in the treatment of epilepsy. Drugs. 2007; *67:* 2231-2256.

[14] *Mula M, Trimble MR.* The importance of being seizure free: topiramate and psychopathology in epilepsy. Epilepsy Behav. 2003; *4:* 430-434.

[15] *Nayak R, Gisclon L, CA.* C et al. Estimation of the absolute bioavailability of topiramate in humans without intravenous data. J Clin Pharmacol. 1994; *34:* 1029.

[16] *Park J, Park Y-S, Min-Ho Lee, Si-Youn Rhim, Jae-Chul Song, Soo-Jin Lee, Jung-Mogg Kim, Leslie M Shaw, Kang J-S.* Determination of plasma topiramate concentration using LC-MS/MS for pharmacokinetic and bioequivalence studies in healthy Korean volunteers. Biomedical Chromatography. 2007; *22:* 822-829.

[17] *Privitera M.* Generic antiepilectic dryg: current controversies and future directions. Current Review in Clinical Science. 2008; *8:* 113-117.

[18] *Ramsay RE, Uthman B, Pryor FM, Rowan AJ, Bainbridge J, Spitz M, Sirven JI, Frederick TE.* Topiramate in older patients with partial-onset seizures: a pilot double-blind, dose-comparison study. Epilepsia. 2008; *49:* 1180-1185.

[19] *Sachdeo RC, Reife RA, Lim P, Pledger G.* Topiramate monotherapy for partial onset seizures. Epilepsia. 1997; *38:* 294-300.
[20] *Sachdeo RC, Sachdeo SK, Walker SA, Kramer LD, Nayak RK, Doose DR.* Steady-state pharmacokinetics of topiramate and carbamazepine in patients with epilepsy during monotherapy and concomitant therapy. Epilepsia. 1996; *37:* 774-780.
[21] *Schuirmann DJ.* A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm. 1987; *15:* 657-680.
[22] *Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE.* An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia. 2000; *41 (Suppl):* 3-9.
[23] *Shank RP, Maryanoff BE.* Molecular pharmacodynamics, clinical therapeutics, and pharmacokinetics of topiramate. CNS Neurosci Ther. 2008; *14:* 120-142.
[24] *WHO.* Multisource (Generic) Pharmaceuticals Products: Guidelines On Registration Requirements to Establish Interchangeability, WHO Expert Committee On Specifications for Pharmaceutical Preparations, Geneva; 1996.
[25] *WHO.* Technical Report Series. Guidelines on registration requirements to establish interchangeability. Vol 937; 2006.
[26] *Yen DJ, Yu HY, Guo YC, Chen C, Yiu CH, Su MS.* A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy. Epilepsia. 2000; *41:* 1162-1166.
[27] *Garnett WR.* Clinical pharmacology of topiramate: a review. Epilepsia. 2000; *41 (Suppl):* 61-65.