Interchangeability of generic anti-epileptic drugs: a quantitative analysis of topiramate and gabapentin

Marc Maliepaard · Nikola Banishki · Christine C. Gispen-de Wied · Steven Teerenstra · André J. Elferink

Abstract

Purpose The objective of this study was to determine whether the so-called "shift" or "drift" problem might occur when generic anti-epileptic drugs are interchanged, and thus to assess if generic anti-epileptic drugs are interchangeable and can be used in an efficacious and safe way on the basis of their bioequivalence to one and the same reference product.

Methods The bioequivalence of topiramate and gabapentin generics was evaluated. For proper interstudy comparison, individual exposure data (AUC and C_{max}) for each bioequivalence study present in the registration dossier was normalized based on the absolute exposure data of one of two innovators. The exposure-normalized plasma concentration curves of the generic product arms between studies were compared, providing indirect evidence of bioequivalence of the different generics. Additionally, comparisons were made for generic–generic as well as innovator–innovator exchange based on absolute exposure data from individual bioequivalence studies.

Results In almost all cases, estimated 90% confidence intervals of the AUC and C_{max} ratios for generic–generic interchange were within the routine 80–125% criterion. When absolute, non-corrected exposure data were used for this interstudy comparison, in a number of cases 90% confidence intervals outside the 80–125% criterion were found upon interchanging generics from two studies. However, a similar pattern of 90% confidence intervals outside the 80–125% criterion was observed for the comparison of innovator arms, despite the fact that the innovator was identical in all studies.

Conclusion Our results strongly indicate that the so-called drifting problem upon generic–generic substitution does not result in important differences in exposure upon exchanging topiramate generics or gabapentin generics.

Keywords Bioequivalence · Drifting problem · Epilepsy · Anti-epileptic generic drugs

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Introduction

Upon development and initial marketing authorization, new pharmaceutical formulations receive a 10-year period of data protection. Following the expiry of this protection period, various new generic agents using the innovator's active substance appear on the market. For such generics, no new clinical trials are required, whereas authorization is in most cases granted solely on the proof of bioequivalence after a single-dose controlled trial comparing the generic with the innovator product. If proven to be bioequivalent, the generic product is considered therapeutically equivalent

to the innovator formulation [1, 2]. Official regulations regarding generic products require tests to establish whether the pharmacokinetic parameters AUC and C_{max} are within established limits compared with the same parameters of the innovator.

Under current regulations, the testing of the relative exposure of a generic against exposure obtained with other generics is not required. However, due to the unavailability of such data, a so-called "shift" or "drift" problem may occur when generics are interchanged, and is a reason for concern [3]. While generics are interchangeable with the innovator product, generics themselves may not be, thereby possibly causing loss of efficacy and/or toxicity. The problem may become relevant for certain drugs with a narrow therapeutic window, including anti-epileptic drugs. Seizure control may be lost or anti-epileptic plasma levels may be increased, causing toxicity, when such a drift would indeed occur if patients switch from one generic to another.

Published studies predict, through various simulation methods, the potential of "drift" between generic formulations. Results from these predictive analyses indicate that the drift problem proportionally increases with the number of generic formulations released and the deviation from unity of the actually observed 90% confidence intervals [3]. Other potential problems associated with switching between generic medications include the use of dissimilar excipients, the different appearance of the formulations, and different product names, the latter two factors possibly resulting in changes in patient adherence patterns [4, 5].

In epidemiological terms, epilepsy is a common chronic disorder affecting about 50 million people worldwide with 200,000 new cases every year, therefore representing a significant part of any country's public healthcare program [6, 7]. The use of generics in epilepsy is subject to intensive debate. This debate relates to, for example, bioequivalence requirements, possible difference in variability in exposure and consequences of small differences, problems with medicine supply, and possible legal consequences when patients do not provide explicit permission for being switched to a generic medicine [8–12]. It is unclear what the consequences are in terms of adverse events, and thus the costs for society and the consequences for the individual patient [13].

Epilepsy is an area in which many generics are available. Recently, we discussed the available evidence that generic interchange of anti-epileptic drugs does indeed lead to significant differences in exposure [14]. It appeared that only on very rare occasions, a relevant reduced exposure was reported upon switching to a generic anti-epileptic drug [11]. Other reported data suggesting both upward and downward difference in exposure upon generic substitution were in fact only able to show difference in exposure when other factors besides generic exchange (e.g., different dose,

exchange with a different type of formulation) were present [15]. A number of published surveys [16–18] as well as observational studies [19, 20] suggest a difference in epilepsy-related adverse events after switching from branded to generic anti-epileptics. However, these studies do not provide evidence for real differences in exposure, or for a causal relationship between generic substitution and, for example, the occurrence of seizures. It was therefore concluded that at present no evidence is available to support the hypothesis that differences in exposure are responsible for adverse events observed upon generic exchange of anti-epileptic drugs [14]. This conclusion is also apparent in a recent meta-analysis by Kesselheim et al. In this analysis, the apparent increase in seizures obtained purely from observational studies is proposed to be explained by undue worries from patients or physicians about the effectiveness of generic anti-epileptic drugs after a switch [21].

The present study focuses on the possible consequences of generic–generic exchange for relative exposure, and for that reason compares different topiramate (Topamax®) and gabapentin (Neurontin®) generics that are currently registered in The Netherlands in an attempt to quantify possible differences in bioavailability when exchanging different generics. Data were obtained from the generics' registration files as available from the Dutch Medicines Evaluation Board (referred to as the Agency), and analyzed according to current methodological and statistical principles [14].

Materials and methods

Data collection

The data used in this study were obtained from bioequivalence studies submitted for the topiramate and gabapentin generic products that were registered in January 2008. All data were available and accessible through the Agency's database.

Our interstudy comparison of topiramate exposure focused on the relative exposure obtained by administration of 200 mg, since in almost all cases, bioequivalence in the registration file was indeed demonstrated using a 200-mg dose. For gabapentin, exposure was compared at the 400-mg, 600-mg, and 800-mg levels. In all cases, registration of each individual strength was supported by a bioequivalence study at that strength.

In each bioequivalence trial, the same innovator product was used, i.e., Topamax® (Janssen-Cilag) for topiramate, and Neurontin® (Pfizer) for gabapentin. Actually measured plasma concentrations varied between different bioequivalence studies, a known phenomenon that is most likely due to differences in study design, e.g., different volunteers

(with regard to, for example, age, ethnicity, weight, etc.), different sampling times, or different laboratories applying different analysis methodologies.

The 200-mg Topamax® mean AUCs in the included bioequivalence studies ranged from 125.3 to 158.6 μg*h/ml, and C_{max} from 4.17 to 5.05 μg/ml. Likewise, Neurontin® mean AUCs ranged from 25.9 to 33.8 μg*h/ml, and C_{max} from 1.00 to 1.15 μg/ml for the 400-mg strength, from 41.3 to 47.6 μg*h/ml and from 1.36 to 1.58 μg/ml for the 600-mg strength, and from 37.0 to 56.9 μg*h/ml and from 1.28 to 1.77 μg/ml for the 800-mg strength.

Normalization of the absolute exposure data

In order to ensure uniformity of the study-to-study comparison and avoid bias due to differences in actual plasma exposure between different bioequivalence source studies, the innovator arm in each bioequivalence study was used to correct for any absolute difference in the generic arms. For this purpose, the average of the mean AUC_{0-t} and C_{max} of all innovator arms was calculated and the study with the closest to average value was used as a reference standard. Subsequently, the absolute AUC and C_{max} of each generic was corrected using the ratio of the reference standard vs the innovator AUC and C_{max} of the bioequivalence study in question. By applying this correction, generic exposure was normalized, allowing more reliable interstudy comparisons. After this normalization, the 90% confidence intervals were estimated.

Estimation of the 90% confidence interval for the relative exposure

Ninety percent confidence intervals were calculated using standard methodology for calculating a confidence interval for a difference between means. Details of this methodology are shown in the supplementary material.

Results

Topiramate (Topamax®)

In January 2008, 13 different 200-mg generic topiramate products were registered in The Netherlands. Registration of a number of these generics was based on the same dossier, i.e., the approval of these 13 generic topiramate products was based on 7 different bioequivalence studies, each applying a 200-mg dose. A summary of the actual point estimates and 90% confidence intervals for the AUC and C_{max} ratios of topiramate generics in all available bioequivalence studies is provided in Table 1. The mean point estimate for the AUC ratio for all evaluated studies was 101.16%, and 99.55% for

the C_{max} ratio. The mean absolute deviation of the point estimate from unity for all evaluated studies was 1.16% for the AUC ratio, and 3.52% for the C_{max} ratio.

Seven available bioequivalence studies allowed for 21 generic–generic interstudy comparisons. Indirectly estimated point estimates and 90% confidence intervals for these comparisons using the exposure-normalized data are summarized in Table 2. Figure 1 graphically represents the 90% confidence intervals for the exposure-normalized data for the AUC_{0-t} and C_{max} ratio. For all topiramate generic–generic comparisons, 90% confidence intervals obtained using exposure-normalized AUC and C_{max} values were within the 80–125% range. The mean point estimate for the AUC ratios was very close to 100%, i.e., 100.38%, and 96.62% for the C_{max} ratio. The mean of the absolute deviation of the point estimate from unity for all evaluated studies was 2.21% for AUC, and 4.53% for C_{max}.

Comparison of the absolute, not-normalized AUC and C_{max}, both for the generic and the innovator Topamax®, yielded a number of 90% confidence intervals outside the 80–125% range for bioequivalence. However, in this case a very similar pattern of 90% confidence intervals was observed for the generic–generic and innovator–innovator exchange, despite the fact that the innovator Topamax® was identical in all studies (Figure shown in the Appendix).

Gabapentin (Neurontin®)

In The Netherlands, Neurontin is registered as 100-, 300- or 400-mg capsules, and as 600- or 800-mg tablets. Since gabapentin pharmacokinetics is nonlinear [22], separate bioequivalence studies for each strength have been submitted for the 400-, 600- and 800-mg strengths in support of generic applications. As was the case with topiramate generics, for gabapentin generics, a number of applications were based on the same dossier, i.e., registration of eight 400-mg strengths, five 600-mg strengths, and five 800-mg strengths was based on in total 4 bioequivalence studies per strength. Since per dose strength (i.e., 400, 600, and 800 mg) 4 bioequivalence studies were available, 6 comparisons per dose strength were possible.

Table 3 shows a summary of the actual 90% confidence intervals for gabapentin AUC and C_{max} ratios in the studies submitted to the Agency in support of an application for a generic gabapentin formulation. The mean point estimates for the AUC ratios for all evaluated 400-, 600- and 800-mg studies were very close to 100%, i.e., 100.2%, 102.7%, and 100.2% respectively, and 100.6%, 103.6%, and 97.7% for the C_{max} ratios respectively. The mean of the absolute deviation of the ratio from unity for all evaluated 400-mg, 600-mg, and 800-mg studies was 1.48%, 3.18%, and 3.55% for AUC respectively, and 2.63%, 5.03% and 4.20% for C_{max}.

Table 1 Point estimates and 90% confidence intervals for AUC_{0-t} and C_{max} ratios of registered generic topiramate formulations in The Netherlands

Study number	AUC_{0-t}			C_{max}		
	Statistical parameters			Statistical parameters		
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
1	98.41	100.70	102.94	90.39	96.75	103.45
2	97.07	100.03	103.08	90.14	95.22	100.58
3	101.31	104.15	107.06	100.04	105.59	111.46
4	98.37	100.23	102.12	89.02	94.11	99.49
5	98.70	101.07	103.50	97.20	102.00	109.50
6	98.00	101.00	104.00	95.00	100.00	105.00
7	97.55	100.93	104.42	97.00	103.19	109.78
Mean	98.49	101.16	103.87	94.11	99.55	105.61
SD	1.36	1.38	1.59	4.27	4.32	4.74
Minimum	97.07	100.03	102.12	89.02	94.11	99.49
Maximum	101.31	104.15	107.06	100.04	105.59	111.46
Mean deviation point estimate from unity		1.16%			3.52%	

Point estimates and 90% confidence intervals per dose for each generic–generic interstudy comparison using exposure-normalized data are summarized in Fig. 2 and Table 4. In the vast majority of cases 90% confidence intervals were within the 80–125% margin for bioequivalence, except the C_{max} ratio for G1/G4 with a lower end of the 90% confidence interval of 79.03%, the C_{max} ratio for G5/G7 and G6/G7 with a high end of the 90% confidence interval of 125.45% and 125.75% respectively, and the AUC ratio for G10/G11, with a high end of the 90% confidence interval of 127.62%.

Comparison of the absolute, not-normalized AUC and C_{max} yielded a number of 90% confidence intervals for many generic–generic comparisons outside the 80–125% range for bioequivalence. However, a similar pattern of 90% confidence intervals was noted with generic–generic exchange and innovator–innovator exchange (Figure shown in the Appendix).

Discussion

In this study, exposure data obtained from bioequivalence studies were used in order to indirectly estimate 90% confidence intervals for generic–generic substitution. It appeared that absolute plasma levels obtained with the innovator drugs, i.e., Topamax® and Neurontin®, varied markedly among different bioequivalence studies. This is a known phenomenon that is most likely due to differences in study design, e.g., different volunteers (with regard to, for example, age, ethnicity, weight, etc.), different sampling times, or different laboratories applying different analysis methodologies that are used in the individual bioequivalence studies. Still, this variation impedes direct interstudy comparison and calculation of the 90% confidence intervals for AUC and C_{max} ratios. Indeed, a large variation in 90% confidence intervals was observed applying the absolute, uncorrected AUC and C_{max} from different bioequivalence studies for calculation of the generic–generic 90% confidence intervals. However, a very comparable pattern of 90% confidence intervals was obtained when indirectly estimating 90% confidence intervals for innovator–innovator exchange (see Appendix for Figures). This finding appears paradoxical for the innovator, since in all bioequivalence studies the same innovator product was used, and therefore the 90% confidence intervals for the innovator–innovator exchange would theoretically be expected to be within the 80–125% criterion for bioequivalence. The fact that the 90% confidence intervals for innovator–innovator comparisons were variable in an analogous manner to that observed for generic–generic exchange indicated that this variation is not due to actual formulation-related differences in exposure, but was related to the above-mentioned interstudy differences.

Considering all the bioequivalence studies assessed in this interstudy comparison, the mean point estimates obtained for the topiramate or gabapentin AUC and C_{max} ratios were very close to 100%. The absolute differences in mean bioavailability of the various generic topiramate and gabapentin formulations are relatively low, below 3.55% for AUC_{0-t} and 5.03% for C_{max}. These absolute deviations are very much in line with those observed in a recently published FDA examination, using data from more than 2,000 bioequivalence studies of the FDA. In the FDA

Table 2 Indirectly estimated point estimates and 90% confidence intervals for the exposure-normalized AUC_{0-t} and C_{max} ratios for topiramate generics. G1/G2 represents comparison of generic product from Study 1 with that of Study 2, etc.

| Comparison | AUC_{0-t} | | | C_{max} | | |
| | Indirectly estimated statistical parameter | | | Indirectly estimated statistical parameter | | |
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
G1/G2	90.30	100.51	111.88	89.68	101.53	114.94
G1/G3	87.90	96.87	106.76	89.56	102.08	116.34
G1/G4	92.74	100.15	108.15	91.47	102.72	115.35
G1/G5	90.89	99.62	109.19	83.32	93.68	105.33
G1/G6	88.34	99.41	111.88	86.27	96.54	108.04
G1/G7	89.22	99.65	111.30	82.99	94.06	106.60
G2/G3	87.83	96.38	105.75	90.66	100.54	111.50
G2/G4	91.89	99.64	108.04	91.74	101.18	111.59
G2/G5	90.25	99.11	108.84	83.86	92.27	101.53
G2/G6	88.62	98.90	110.38	86.75	95.09	104.24
G2/G7	89.05	99.14	110.38	83.64	92.64	102.62
G3/G4	102.46	110.29	118.72	90.37	100.63	112.05
G3/G5	94.45	102.84	111.96	82.27	91.78	102.38
G3/G6	102.42	113.14	124.98	85.32	94.58	104.84
G3/G7	85.34	94.07	103.69	82.12	92.15	103.40
G4/G5	93.11	99.47	106.27	82.27	91.20	101.10
G4/G6	90.66	99.26	108.68	85.21	93.99	103.67
G4/G7	91.63	99.50	108.05	82.07	91.57	102.16
G5/G6	89.96	99.79	110.69	93.60	103.06	113.47
G5/G6	90.85	100.03	110.13	90.19	100.40	111.77
G6/G7	89.24	100.24	112.59	87.91	97.43	107.97
Mean	91.29	100.38	110.40	86.73	96.62	107.66
SD	4.23	4.16	4.55	3.77	4.25	5.06
Minimum	85.34	94.07	103.69	82.07	91.20	101.10
Maximum	102.46	113.14	124.98	93.60	103.06	116.34
Mean deviation point estimate from unity		2.21%			4.53%	

study, the mean absolute difference in bioavailability in these 2,000 studies was 3.56% and 4.35% for AUC and C_{max} respectively [23]. This outcome further strengthens the position that generics will yield comparable efficacy and safety to the innovator formulation [24]. Furthermore, these comparable results between the generics registered in The Netherlands and by the FDA respectively are to be expected, as requirements for generics in the USA and the EU are comparable.

Results obtained upon comparison of the exposure-normalized generic exposure data indicate that for both topiramate and gabapentin, exchanging between different generics in almost all cases results in 90% confidence intervals of the AUC and C_{max} ratios within the routine 80–125% range. Only in 4 out of 36 cases did the gabapentin–gabapentin 90% confidence intervals outer margin marginally exceed the 80–125% acceptance range, i.e., by yielding margins for the C_{max} ratio of 79.03%, 125.45%, and 125.75%, and 127.62% for the AUC ratio.

Although in isolated cases the estimated 90% confidence intervals upon generic–generic exchange were indeed outside the 80–125% margin that is accepted for generics, it should be considered that the estimated generic–generic 90% confidence intervals are wider than those obtained in a direct head-to-head comparison between generics. This is because the indirect comparison applied in this investigation not only includes intraindividual variability, but also interindividual variability (see the Data analysis section in the Appendix). Indeed, the width of the 90% confidence interval for the between group analysis was, on average, a factor 3 larger than the 90% confidence intervals based on the within-subjects comparisons. Therefore, our method can be

Fig. 1 Indirectly estimated 90% confidence intervals of the AUC and C_{max} ratios using exposure-normalized AUC_{0-t} (*top*) and C_{max} (*bottom*) for topiramate generics. The comparisons are represented on the x-axis, e.g., G1/G2 indicates the comparison of generic product used in Study 1 with the generic used in Study 2. The *green* area indicates the bioequivalence acceptance limits of the 90% confidence interval range of 80–125%
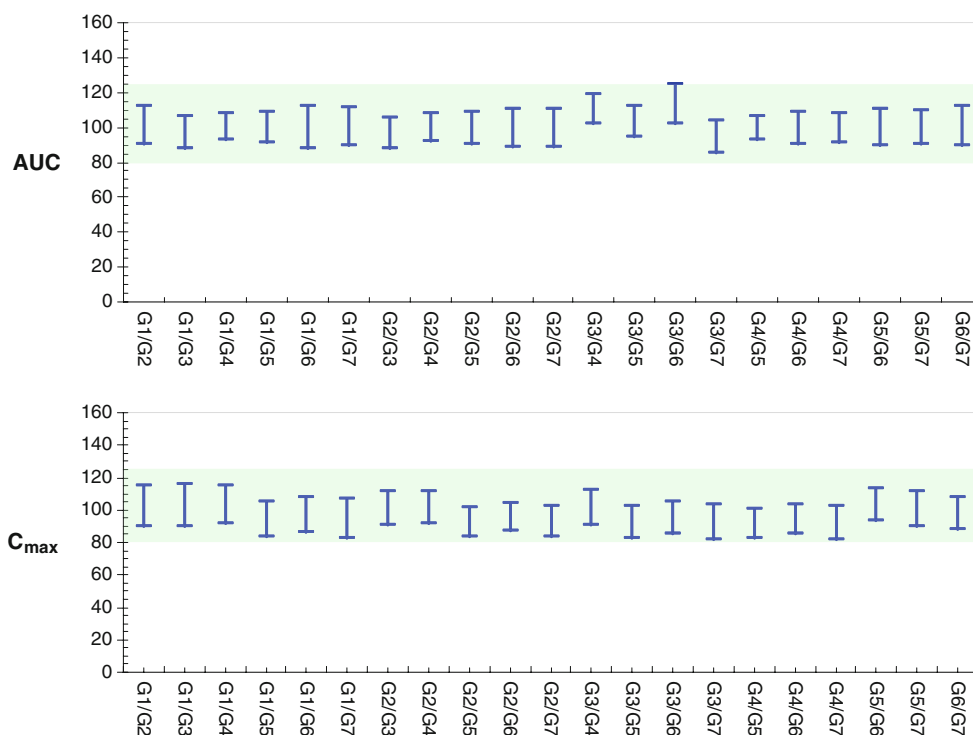
considered a conservative approach. An advantage of this conservative method is that when this indirectly estimated 90% confidence interval meets the 80–125% requirement, it is very unlikely that an actual 90% confidence interval obtained with intrastudy analysis will not meet the 80–125% standard. On the other hand, the 80 or 125% border will be crossed more easily with this indirect comparison than would occur with analysis based on intrastudy evaluations.

An advantage of our interstudy comparison is that the comparison is based on actual rather than theoretical exposure data. Therefore, the data are expected to represent the actual variability in exposure. Limitations of this interstudy comparison are that the relative exposure was estimated via an interstudy comparison, and was based on historical data present in the registration files. Furthermore, only topiramate and gabapentin data have been used in this interstudy comparison, results may not be valid for other medicinal products. Further investigation into this matter is therefore warranted. Moreover, confirmation of these data may come from a multiple arm clinical crossover study comparing multiple generic products with a single innovator product. Both types of investigations have been initiated at the Agency.

Another limitation of our study is that although our data indicate that generic–generic interchangeability is not expected to yield significant differences in exposure on a population level, it cannot be excluded that on an individual basis, exposure is different between the innovator and the generic, e.g., because of different intraindividual variability for the innovator and generic drugs. In order to clarify this aspect, intraindividual variability should be determined, for which a replicate cross-over design study, comparing multiple administrations of the innovator and the generic product, is needed. However, although such replicate design data are not available, it was noted that in all individual bioequivalence studies in our database, both for topiramate and gabapentin, the overall variation of exposure in the individual studies was comparable for the innovator and the generic. Therefore, no clear indication of possible differences in intraindividual variation in exposure is apparent from the data.

Furthermore, in this study the 80–125% acceptance was applied. This criterion is in line with the currently used criterion for assessment of new applications for generic anti-epileptics. However, in the current debate, one issue is the question whether anti-epileptic drugs should be considered a narrow therapeutic index drug, since significant differences in adverse events after relatively small differences in exposure are expected [13, 25].

The current data search of the Agency's database also highlighted the existence of pseudo-variability of generic AEDs on the Dutch market, and probably on other markets as well. Thirteen topiramate and 18 gabapentin generic products are available on the Dutch market, but the registration of many of them is based on the same bioequivalence study, and as such these generics are in fact identical products. Therefore, the number of

Table 3 Point estimates and 90% confidence intervals for AUC_{0-t} and C_{max} ratios of registered 400-, 600-, and 800-mg gabapentin formulations in The Netherlands

Dose	Statistical parameters			Statistical parameters		
	AUC_{t-1}			C_{max}		
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
400 mg						
Study 1	91.0	101.4	111.7	92.5	103.0	113.5
Study 2	91.4	97.4	103.7	90.0	96.0	102.3
Study 3	94.0	101.0	108.0	93.6	101.0	108.0
Study 4	94.4	100.9	108.2	93.9	102.5	111.9
Mean	92.7	100.2	107.9	92.5	100.6	108.9
SD	1.7	1.9	3.3	1.8	3.2	5.0
Minimum	91.0	97.4	103.7	90.0	96.0	102.3
Maximum	94.4	101.4	111.7	93.9	103.0	113.5
Mean deviation point estimate from unity		1.48%			2.63%	
600 mg						
Study 5	97.4	104.6	112.3	100.4	108.4	117.0
Study 6	89.8	99.0	109.2	87.3	97.2	108.1
Study 7	94.6	103.4	113.1	97.8	107.4	118.0
Study 8	95.8	103.7	112.2	92.4	101.5	111.4
Mean	94.4	102.7	111.7	94.5	103.6	113.6
SD	3.3	2.5	1.7	5.8	5.3	4.7
Minimum	89.8	99.0	109.2	87.3	97.2	108.1
Maximum	97.4	104.6	113.1	100.4	108.4	118.0
Mean deviation point estimate from unity		3.18%			5.03%	
800 mg						
Study 9	91.0	100.0	110.0	90.0	98.0	108.0
Study 10	97.4	107.4	118.4	94.9	103.8	113.6
Study 11	87.6	96.8	106.9	86.8	96.8	107.9
Study 12	85.9	96.4	107.2	80.9	92.2	105.2
Mean	90.5	100.2	110.6	88.2	97.7	108.7
SD	5.1	5.1	5.4	5.9	4.8	3.5
Minimum	85.9	96.8	106.9	80.9	92.2	105.2
Maximum	97.4	107.4	118.4	94.9	103.8	113.6
Mean deviation point estimate from unity		3.55%			4.20%	

marketed generics that are really different is less than expected, as many identical generics exist solely for economic reasons, i.e., dossiers are sold between companies and/or products are imported from different EU countries. In those cases, the generics exist with different packaging/appearance whereas the formulations are actually identical. Although this limits the real number of different generics, it is at present virtually impossible for pharmacists and prescribers to identify generics that are actually registered based on a similar/identical dossier.

Our results strongly indicate that the so-called drifting problem upon generic–generic substitution is limited in clinical practice, i.e., does not result in important differences in exposure upon exchanging topiramate generics or gabapentin generics. The data obtained from this comparison may relieve some concerns in the field related to generic–generic substitution, and are therefore considered valuable information in the discussion on the issues surrounding generic–generic substitution. However, it is acknowledged that this conclusion is based on a between-study comparison with a limited number of medicinal products, and further confirma-
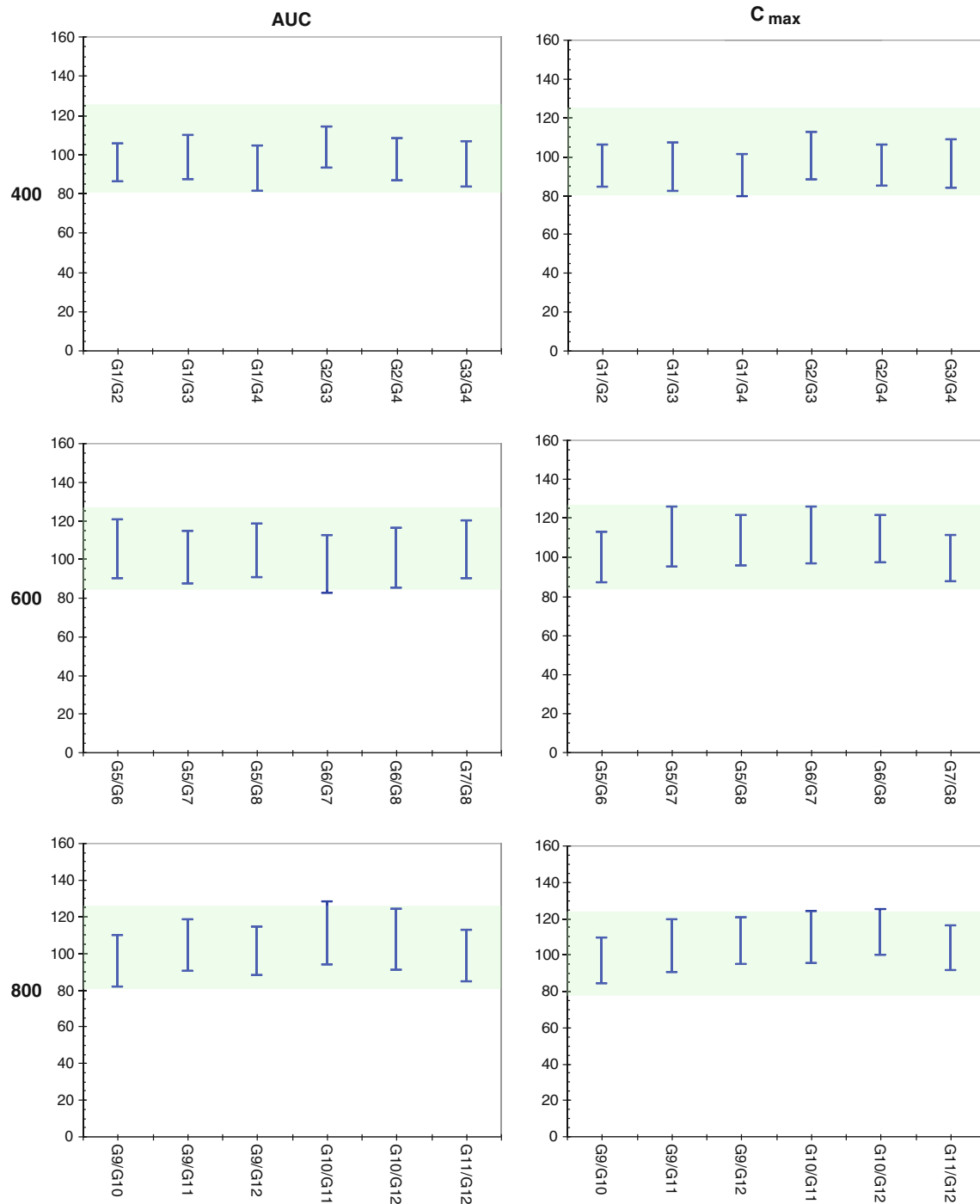
Fig. 2 Indirectly estimated 90% confidence intervals of the AUC and C_{max} ratios comparing the exposure-normalized AUC_{0-t} (*left figures*) and C_{max} (*right figures*) for gabapentin 400-mg, 600-mg, and 800-mg generics (*top, middle, bottom*). The comparisons are represented on the x-axis, e.g., G1/G2 indicates the comparison of the generic product used in Study 1 with the generic used in Study 2. The *green* area indicates the bioequivalence acceptance limits of the 90% confidence interval range of 80–125%

tion of these data may come from more extensive interstudy comparisons, as well as a replicate cross-over design study, or multiple arm clinical crossover study comparing multiple generic products with a single innovator product, the latter study allowing for a direct intrastudy comparison of the relative bioavailabilities of different generics.

Conclusion

Our results, based on indirect comparison of relative exposure, strongly indicate that the so-called drifting problem upon generic–generic substitution does not result in major differences in exposure for topiramate and gabapentin generics.

Table 4 Indirectly estimated point estimates and 90% confidence intervals using exposure-normalized AUC_{0-t} and C_{max} ratios for gabapentin generics. G1/G2 represents comparison of generic product from Study 1 compared to that of Study 2, etc

Dose	Indirectly estimated statistical parameter			Indirectly estimated statistical parameter		
	AUC_{0-t}			C_{max}		
	Lower limit	Point estimate	Upper limit	Lower limit	Point estimate	Upper limit
400 mg						
Comparison G1/G2	85.72	94.96	105.19	84.23	94.29	105.57
Comparison G1/G3	86.92	97.67	109.75	81.76	93.58	107.11
Comparison G1/G4	81.03	91.79	103.98	79.03	89.26	100.81
Comparison G2/G3	93.13	102.85	113.59	87.71	99.24	112.30
Comparison G2/G4	86.66	96.67	107.83	84.75	94.66	105.73
Comparison G3/G4	83.08	93.98	106.32	83.67	95.38	108.73
Mean	86.09	96.32	107.78	83.52	94.40	106.71
SD	4.13	3.81	3.49	2.93	3.21	3.81
Minimum	81.03	91.79	103.98	79.03	89.26	100.81
Maximum	93.13	102.85	113.59	87.71	99.24	112.30
Mean deviation point estimate from unity		4.63%			5.60%	
600 mg						
Comparison G5/G6	89.87	104.02	120.41	86.76	98.93	112.81
Comparison G5/G7	87.20	99.80	114.22	94.77	109.03	125.45
Comparison G5/G8	90.56	103.41	118.08	95.48	107.51	121.06
Comparison G6/G7	82.07	95.94	112.16	96.59	110.21	125.75
Comparison G6/G8	85.15	99.41	116.06	97.24	108.67	121.44
Comparison G7/G8	89.65	103.62	119.75	87.52	98.60	111.09
Mean	87.41	101.03	116.78	93.06	105.49	119.60
SD	3.31	3.20	3.23	4.67	5.28	6.26
Minimum	82.07	95.94	112.16	86.76	98.60	111.09
Maximum	90.56	104.02	120.41	97.24	110.21	125.75
Mean deviation point estimate from unity		2.65%			6.32%	
800 mg						
Comparison G9/G10	81.61	94.46	109.34	83.82	95.58	108.99
Comparison G9/G11	90.10	103.12	118.03	90.01	103.56	119.15
Comparison G9/G12	87.71	100.16	114.37	94.68	106.61	120.05
Comparison G10/G11	93.38	109.17	127.62	94.96	108.35	123.63
Comparison G10/G12	90.82	106.03	123.79	99.81	111.54	124.66
Comparison G11/G12	84.04	97.13	112.25	91.38	102.95	115.99
Mean	87.94	101.68	117.57	92.44	104.77	118.74
SD	4.43	5.52	7.01	5.42	5.50	5.72
Minimum	81.61	94.46	109.34	83.82	95.58	108.99
Maximum	93.38	109.17	127.62	99.81	111.54	124.66
Mean deviation point estimate from unity		4.48%			6.24%	

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