REVIEW

Requirements for generic anti-epileptic medicines: a regulatory perspective

Marc Maliepaard · Yechiel A. Hekster · Arnoud Kappelle ·
Eugène P. van Puijenbroek · André J. Elferink · Jan Welink ·
Christine C. Gispen-de Wied · Frits J. F. Lekkerkerker

Introduction

Currently, there is a lot of discussion about whether generic substitution of anti-epileptic medicines with the same active moiety but from different manufacturers can take place safely. Issues raised in this discussion relate to bio-equivalence requirements, variability in exposure, problems with medicine supply, costs of adverse events, and possible legal consequences when patients do not provide explicit permission for being switched to a generic medicine [2–6]. Furthermore, it is not clear what the

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M. Maliepaard (✉)
MEB-CBG/Radboud University Medical Centre, 579,
P.O. Box 9101, 6500 HB Nijmegen, The Netherlands
e-mail: m.maliepaard@cbg-meb.nl

Y. A. Hekster
Department of Clinical Pharmacy, Radboud University Medical
Centre, Nijmegen, The Netherlands

A. Kappelle
Department of Neurology, Radboud University Medical Centre,
Nijmegen, The Netherlands

E. P. van Puijenbroek
Analysis Department, Lareb, 's-Hertogenbosch, The Netherlands

J. Welink · F. J. F. Lekkerkerker
MEB-CBG, The Hague, The Netherlands

A. J. Elferink · C. C. Gispen-de Wied
Pharmacotherapeutic Department CN Products, MEB-CBG,
The Hague, The Netherlands

consequences are in terms of adverse events, and thus the costs for society and the consequences for the individual patient [7].

In most countries, generic substitution is the principal responsibility of the delivering pharmacist. In a recently published statement, the American Academy of Neurology argues that in their opinion the permission of both the prescribing physician and the patient should be necessary before generic substitution is allowed to take place [8]. Analogously, the Netherlands Society of Neurology and the Dutch League Against Epilepsy state that such exchange requires careful guidance of and information to the patient and possibly consultation with the prescribing physician. Furthermore, they state the importance of continuity of delivery of the same product (either for generic or for branded medicines) for this group of patients [9]. It is understandable that in clinical practice concerns are expressed related to generic anti-epileptic medicines. After all, many anti-epileptics are medicines with a narrow therapeutic index. Besides, the consequences of an epileptic attack are severe, in a physical, psychological and social respect. Therefore, there is ample ground to look critically at generic substitution of anti-epileptic medicines. The Dutch regulatory agency MEB-CBG attaches significance to this issue and considers this discussion of the utmost importance. As a contribution to this discussion, this position paper considers the conditions with which generic substitution should comply in order to be safe and effective.

Generic is exchangeable

When the patent or legal protection period of a medicinal product has expired, it is possible to apply for marketing a

generic version of that medicine. Thus, a situation develops in which patients are no longer treated with the original branded medicine (specialité, innovator), and *generic substitution* occurs. This implies that the branded medicine is replaced by a medicine with an identical active moiety. Besides generic substitution, we also recognize *therapeutic substitution*. Therapeutic substitution implies that a medicine is replaced by another medicine from the same therapeutic class, e.g., omeprazole by pantoprazole. It is hard to evaluate this form of substitution as there are hardly any studies that report on it. This type of therapeutic substitution will not be covered in this position paper.

A generic is a medicine containing the same active moiety with the same content and the same pharmaceutical form as the branded medicine (pharmaceutical equivalent). If the generic manufacturer can demonstrate that plasma exposure in time of the generic medicine can be considered equal to that of a branded medicine (i.e., products are considered bioequivalent), the generic is considered therapeutically equivalent. In that case the generic applicant can refer to the investigations presented in the filing for the branded medicine to support its safety and efficacy. The assessment of bioequivalence, and thus therapeutic equivalence, of generic medicines and the branded medicine in the European Community is one of the tasks of the National Medicines Evaluation Boards and the European Medicines Agency (EMEA).

A demonstration of equal plasma exposure in time of two medicines, defined by the area under the plasma concentration–time curve (AUC) and the maximum plasma concentration (C_{max}) is called bioequivalence. The underlying principle of using bioequivalence to declare therapeutic equivalence is that there always ís a relationship between the plasma concentration–time profile and the efficacy and toxicity of a medicinal product. This implies that when the concentration–time profile of the generic active moiety is equal to that of the branded medicine, the efficacy and safety as far as the active moiety is concerned will be the same as well.

In principle, a bioequivalence study is a study with a two-way cross-over design, mostly conducted in healthy volunteers. The volunteers receive the generic and the branded medicines in a randomised sequence, with an appropriate washout period in between. Before and after drug intake, plasma concentrations are determined at regular timepoints. Essential to these studies is that the same active moiety derived from two different formulations (i.e., generic and branded) are compared for the same individual. The individual thus becomes his/her own control. The comparison of the pharmacokinetics of the active moiety should be in strict accordance with European requirements with regard to AUC and C_{max} [10], which are determined

in these studies as a measure for the extent and rate of absorption. The requirements posed in Europe related to bioequivalence are comparable to those in other western countries, such as the USA and Canada. In all cases, the AUC and C_{max} for the generic and branded medicine should equal; more specifically, the 90% confidence interval of the ratio $AUC_{generic}/AUC_{branded}$ and $C_{max-generic}/C_{max-branded}$ should be between 0.80 and 1.25. These limits are based on clinical relevance of potential differences in exposure and are accepted as such internationally [10, 11]. Other issues regarding further regulatory points of attention in the assessment of bioequivalence are that the study is sufficiently powered, that an adequate and validated analytical method is applied, and GCP/GLP conditions are implemented.

The bioequivalence study will reveal whether 'inactive' excipients of a medicinal product play a role in the absorption of the active moiety. If this is the case, concentration–time profiles will differ, and when 90% confidence intervals do not comply with the requirements, registration of the generic medicine is not possible.

Supplementary requirements for bioequivalence studies apply in cases of special formulations, such as products with controlled release. For instance, minimal plasma concentrations (C_{min}), peak-trough fluctuations and a possible food interaction will be included in the assessment. Furthermore, dose-dumping, i.e., the immediate release of the full dose, should be excluded in vivo [11].

Anti-epileptic generics in the EU

Generic formulations are currently available for a number of anti-epileptics. An overview of registered anti-epileptics in the EU is provided in Table 1.

For a number of formulations, such as carbamazepine and valproic acid, different pharmaceutical formulations are marketed. Carbamazepine, for example, is available as an immediate release (IR) and a controlled release (CR) tablet, and valproic acid as an IR, a CR and an enteric coated (EC) formulation. Generics are registered separately for all these formulations, and all these individual generics fulfill the requirements as stated earlier. Since the pharmacokinetics of the active moiety, and thus the efficacy and safety, is influenced by the type of formulation, it is obvious that an IR formulation in principle cannot be exchanged with a CR or EC formulation, nor an EC with an IR or CR formulation. However, substitution to an equivalent formulation of the same active moiety, e.g., substitution from Tegretol® to the carbamazepine IR generic, and from Tegretol CR to the CR generic will result in equal exposure in time and therapeutic equivalence.

Table 1 Branded and generic oral anti epileptic medicines available on the EU market

Active moiety	Branded	Formulation	Generic registered
Carbamazepine	Tegretol	**IR**, tablet, suspension	**Yes**
	Tegretol CR	**CR**, tablet	**Yes**
Clobazam	Frisium	**IR**, tablet	No
Clonazepam	Rivotril	**IR**, tablet	No
Diazepam	Stesolid, Valium a.o.	**IR**, tablet	**Yes**
Ethosuximide	Ethymal	**EC**, capsule,	No
		IR, suspension	
Felbamate	Taloxa	**IR**, tablet, suspension	No
Gabapentin	Neurontin	**IR**, capsule, tablet	**Yes**
Pregabalin	Lyrica	**IR**, capsule	No
Lamotrigine	Lamictal	**IR**, capsule, tablet, dispersible tablet	**Yes**
Levetiracetam	Keppra	**IR**, tablet, oral solution	No
Nitrazepam	Mogadon, Apodorm, Insomin, Remnos, a.o.	**IR**, tablet	**Yes**
Oxcarbazepine	Trileptal	**IR**, tablet, suspension	**Yes**
Phenobarbital	Luminal, Phenobarbital	**IR**, tablet	**Yes**[a]
Phenytoin	Diphantoine	**IR**, tablet	No
Primidone	Mysoline	**IR**, tablet	No
Topiramate	Epitomax, Topamax, Topaz-25	**IR**, tablet, capsule	**Yes**
Valproic acid	Convulex, Depacon, Depakene, Depakine, Depakote, Divalproex, Epiject, Epilim, Epival, Orlept a.o.	**IR**, tablet	**Yes**
		CR, tablet	
		CR, granulate	
		EC, capsule	
Vigabatrin	Sabril	**IR**, tablet, granulate	No
Zonisamide	Zonegran	**IR, capsule**	No

IR immediate release, *CR* controlled release, *EC* enteric coated (gastroresistant)

[a] In some countries no branded medicine on the market

Concerns about generics in daily practise

A frequently expressed worry is that bioequivalence studies are conducted in healthy volunteers rather than in the actual target patient population [5]. However, no data have been published as yet that indicate that relative differences in bioavailability of generic and branded medicines in healthy volunteers would translate to other relative values in the patient population.

This can be understood by considering the basis of generic applications, i.e., the fact that when absorption of the active moiety from the branded and generic medicine is equal (i.e., bioequivalent), further effects in actual patients, in patients with renal or hepatic impairment, in the young and the elderly will be equal as well. In all cases, it is the effects after proven equal absorption which determine this effect, and after absorption of the active moiety in the circulation there is no plausible difference between the active moiety originating from the branded or generic medicine ('the active moiety does not know its origin'). The fact that individual patients may obtain different plasma levels due to differences in metabolism of excretion does not impair this conclusion, because this will be the case both for the branded and the generic medicine to the same extent. The generic and the branded medicine thus remain therapeutically equivalent.

Bioequivalence criteria are sometimes explained as the possibility 'that there could be as much as a 56% increase or a 36% decrease in bioavailability when switching between different generic formulations' [4]. If so, this expectedly would pose a problem, especially for narrow therapeutic drugs. However, using the statistical criteria (90% confidence interval within 0.80–1.25), it is difficult for any generic product whose mean arithmetic bioavailability parameters differ by more than 10% from the reference to meet the confidence interval requirements, and it is virtually impossible to meet the confidence interval requirements if these differences approach 20%. Furthermore, an FDA review demonstrated that the average difference between the bioequivalence of more than 270 generic medicines approved in 1997 and their trade-name counterparts was 3.5% [12]. Although not formally investigated, figures in the European Union will not be too much different from these figures reported by the FDA. Also the

arbitrary choice of a 90% instead of, e.g., a 95 or 99% confidence interval may be fuelling concerns. However, despite this arbitrary decision, the long-term experience with generics world-wide shows that this margin is adequate in a vast majority of the cases to govern effective and safe substitution of generic formulations. Hypersensitivity to certain excipients may occur [7], but is limited to exceptional cases.

Generic–generic substitution also deserves attention. Generics are evaluated by comparison with the branded product. One could argue that generic–generic substitution, which is likely to occur in practice, is not investigated, and may be more prone to bioinequivalent exposure. Based on the average difference in exposure between the branded product and the generic of 3.5% [12] this is a rather remote possibility. The original publication on generic–generic substitution by Anderson et al. [13] indicated that while drifting is possible, in theory, when exchanging two generics with opposite point estimates (e.g., one being <0.90, one being >1.10), these occasions are very rare. Currently, investigations are ongoing within the Dutch Medicines Agency investigating this possibility by comparing the exposure of different generic antiepileptic drugs (i.e., topiramate and gabapentin) obtained from all actually filed bioequivalence studies that led to approval, and estimating the 90% confidence intervals for such substitution. Mean ratios for topiramate AUC and C_{max} from nine filed bioequivalence studies were 1.014 ± 0.014 and 1.000 ± 0.042, respectively. For gabapentin (800 mg), the mean ratio for AUC obtained in three studies was 0.988 ± 0.018, and 0.988 ± 0.25 for C_{max}. Preliminary results of this investigation into generic–generic substitution indicate that in almost all cases the 90% confidence intervals obey the 80–125 margin (Personal communication).

Unfamiliarity with generic medicines, and thus less faith in them, is a well-known phenomenon. This phenomenon, potentially fuelled by possible differences in shape or color between the generic and branded medicine, may initiate doubts in prescribing physicians and patients. When, on top of this, patients are being provided successively with generic medicines from various origins, be it due to a change in purchase policy of the pharmacist or the health insurance company, doubts can be amplified with negative effects on compliance. In our opinion, this aspect certainly deserves the attention of the delivering pharmacist.

The issue of generic antiepileptics is rather old, since a number of generic antiepileptics, e.g., carbamazepine and valproic acid, have been marketed for a long time. Carbamazepine was indeed one of the first generic antiepileptics about which worries were expressed [14]. Because of the concerns at that time, further pharmacokinetic and clinical investigations were conducted on behalf of the Dutch Regulatory Agency, in which the 'older' carbamazepine generic medicines were compared with the branded Tegretol [15, 16]. Results from these investigations demonstrated that pharmacokinetics of carbamazepine and its metabolites were not clinically significantly different for Tegretol and its generics. Moreover, no difference in subjective complaints and cognitive functions was noted between patients using any of these medicines.

Until April 1st, 2008, the Netherlands Pharmacovigilance Centre Lareb (Lareb) has received 2,103 reports mentioning an antiepileptic agent as the suspected drug. In 26 of these reported cases, a possible relationship was indicated between substitution from a branded medicine to a generic one. It is reassuring that a relatively low number of reports was received by Lareb over all these years that indicate problems due to switching from branded antiepileptic drugs to generic ones. It should be required to report al cases of ADRs possibly related to substitution to the national pharmacovigilance centers. Only then can the prescribing physician, pharmacist and patient contribute to an optimal surveillance of generic medicines, and provide the opportunity to pick up signals that may point to problems in clinical practice.

Most literature data on issues regarding switching of antiepileptic medicines is based on surveys. One survey, conducted in Germany, Austria and Switzerland, indicated that 50% of the responding treating neurologists had experienced at least one problem possibly related to substitution of a generic medicine. The relation with an epileptic attack was not mentioned in this study [17]. Also the frequency of switching back from a generic to a branded antiepileptic medicine has been a subject of investigation [18]. Besides the actual findings, results from these studies appear to indicate that the level of acceptance of a generic medicine by the patient, physician and pharmacist plays a vital role in switching. Only in rare occasions was a relevant reduced exposure reported upon switching to a generic antiepileptic drug [5]. Other articles have published results of surveys on problems related to switching to generics [17, 19–21]. However, although these surveys undoubtedly express the opinions of many people involved in generic substitution, these surveys do not provide evidence for real differences and a causal relationship between generic substitution and, for example, the occurrence of seizures. We are of the opinion that survey-type investigations do not provide a good reflection of the reality of a problem. Additional studies should be conducted to establish any differences between brand and generic products. Recently, a case-control study by Zachry et al. [22] indicated that epilepsy patients with an epilepsy event requiring hospitalization, emergency room visit, or ambulance had 81% higher odds of having had a switch to a generic than patients with an epilepsy event requiring an office visit. Of note, most (approximately 40%) of the patients in this study were switched to a zonisamide generic, which is not available yet in the EU. Although this case-control study is

not able to prove causality, these findings certainly deserve follow-up investigations. For such studies, in order to evaluate the impact of the general acceptance level on the judgment of the effect, a randomised and especially blinded setup is required. In this respect the initiative of the American Epilepsy Society to try and initiate such a blinded prospective trial is highly welcomed [23, 24].

Other causes for the occurrence of seizures during antiepileptic treatment

Increased susceptibility to seizures may be due to pharmacokinetic interactions with new comedications or comedication that has been withdrawn. E.g., carbamazepine is metabolized by cytochrome P450 3A4 [25], valproic acid by UDP-glucuronosyltransferase (UGT) 2B7 [26], and phenytoin by cytochrome P450 2C9 [27]. Consequently, the inhibition or induction of these metabolizing agents by comedication is prone to affect the clinical outcome for these antiepileptic medicines. Moreover, many of the antiepileptic medicines have an enzyme inducing effect, which complicates prediction of these kind of pharmacokinetic interactions in clinical practice, in particular when more antiepileptic drugs are being combined, as reviewed by Patsalos et al. [28]. The complexity of such interactions is further illustrated, e.g., by lamotrigine, which is known to interact with the estrogen component of contraceptive agents, an interaction that appears period-dependent [29, 30]. Moreover, these pharmacokinetics are also strongly influenced by pregnancy [31–33], a phenomenon also described for levetiracetam [34].

Besides these pharmacological issues, compliance may also be critical in the occurrence of seizures during antiepileptic treatment. Compliance of epilepsy patients in the course of time has been reported to change, sometimes as a consequence of receiving a generic that is not trusted [35]. In this respect it may be desirable not to enforce a frequent switch between different generic brands, in order to limit possible worries of the patient as much as possible.

Handoko et al. [36] indicated that patients who started, besides their normal anti-epileptic medication, several non-antiepileptic comedications, experienced a 5-times increased chance of an epilepsy-related hospitalization. Although at this moment a causal relationship still needs to be confirmed, it is an illustration of the complexity of the issue. In our opinion, a causal pharmacological relationship between switching to or between antiepileptic generic medicines and the occurrence of seizures is not very likely.

Summary

Bioequivalence requirements are very strict and are the basis of therapeutic equivalence between innovators and generics. Therefore, switching to a generic anti-epileptic medicine appears to be safe based on pharmacokinetic grounds, and does not appear to provide a plausible pharmacological explanation for those cases where seizure frequency or seizure patterns change during antiepileptic treatment. Other causes may contribute, such as pharmacokinetic or pharmacodynamic drug–drug interactions. Another important factor may be lack of compliance, due to poor acceptance of a generic medicine. Frequent switching to other generics could negatively influence compliance and should be avoided.

There is a major discrepancy between the actual number of reported adverse events upon switching and the opinion on this subject in clinical practice. It is crucial that both prescribers and pharmacists report adverse events, in order to allow them to take appropriate action when necessary. By doing so, prescribing physician, pharmacist and patient can contribute to an optimal surveillance of generic medicines, and thus contribute to the wellbeing of the patients at stake.

References

1. Maliepaard M, Hekster YA, Kappelle A (2008) Eisen van het College ter Beoordeling van Geneesmiddelen aan generieke antiepileptica. Tijdschrift voor Neurologie en Neurochirurgie 109:34–40 (in Dutch)
2. Welty TE (2007) Pharmacy and generic substitution of antiepileptic drugs: missing in action? Ann Pharmacother 41:1065–1068
3. Berg MJ (2007) What's the problem with generic antiepileptic drugs? A call to action. Neurology 68:1245–1246
4. Heany DC, Sander JW (2007) Antiepileptic drugs: generic versus branded treatments. Lancet Neurol 6:465–468
5. Burkhardt RT, Leppik IE, Blesi K et al (2004) Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 63:1494–1496
6. Makus KG, McCormick J (2007) Identification of adverse reactions that can occur on substitution of generic for branded lamotrigine in patients with epilepsy. Clin Ther 29:334–341
7. Crawford P, Feely M, Guberman A, Kramer G (2006) Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. Seizure 15:165–176
8. Liow K, Barkley GL, Pollard JR, Harden CL, Bazil CW (2007) Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. Neurology 68:1249–1250
9. Epilepsy. Guideline for diagnostics and treatment. The Netherlands Society of Neurology and the Dutch League against Epilepsy, 2006 (in Dutch)
10. Note for guidance on the investigation of bioavailability and bioequivalence. CPMP/EWP/QWP/1401/98. EMEA, London, 26 juli 2001. http://www.emea.europa.eu/pdfs/human/ewp/140198en.pdf. Accessed 28 May 2009
11. Note for Guidance on the investigation on modified release oral and transdermal dosage forms: section II (Pharmacokinetic and

clinical evaluation). CPMP/EWP/280/96. EMEA, London, 28 juli 1999. http://www.emea.europa.eu/pdfs/human/ewp/028096en.pdf. Accessed 28 May 2009

12. Henney JE (1999) From the Food and Drug Administration. JAMA 282:1995

13. Anderson S, Hauck WW (1996) The transitivity of bioequivalence testing: potential for drift. Int J Clin Pharmacol Ther 34:369–374

14. For and against generic prescribing. Drug Ther Bull 1987;25: 93–95

15. Olling M, Mesinga TT, Barends DM et al (1999) Bioavailability of carbamazepine from four different products and the occurrence of side effects. Biopharm Drug Dispos 20:19–28

16. Aldenkamp AP, Rentmeerster T, Hulsman J et al (1998) Pharmacokinetics and cognitive effects of carbamazepine formulations with different dissolution rates. Eur J Clin Pharmacol 54:185–192

17. Krämer GJ, Steinhoff BJ, Feucht M, Pfäfflin M, May TW (2007) Experience with generic drugs in epilepsy patients: an electronic survey of members of the German, Austrian and Swiss branches of the ILAE. Epilepsia 48:609–611

18. Andermann F, Duh MS, Gosselin A, Paradis PE (2007) Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. Epilepsia 48:464–469

19. Wilner AN (2004) Therapeutic equivalency of generic antiepileptic drugs: results of a survey. Epilepsy Behav 5:995–998

20. Berg MJ, Gross RA (2006) Physicians and patients perceive that generic drug substitution of anti-epileptic drugs can cause breakthrough seizures—results from a U.S. survey. First North American Regional Epilepsy Congress: 60th Annual Meeting of the American Epilepsy Society; December 1–5; San Diego, CA. Abstract 2.105

21. Markus K (2006) Generic substitution of antiepileptic drugs—preliminary observational reports of lamotrigine switching in Canada. First North American Regional Epilepsy Congress: 60th Annual Meeting of the American Epilepsy Society; December 1–5; San Diego, CA. Abstract 2.219

22. Zachry WMIII et al (2008) Case-control analysis of ambulance, emergency room, or inpatient hospital events for epilepsy and antiepileptic drug formulation changes. Epilepsia 50:493–500

23. AES calls for definitive study to examine antiepileptic drug substitution. Cassels C. Medscape Medical News 2007. http://www.medscape.com/viewarticle/566840. Accessed 28 May 2009

24. AES. The substitution of different formulations of antiepileptic drugs for the treatment of epilepsy. http://www.aesnet.org/index.cfm?objectid=77B10758-E7FF-0F41-2C82BE234AB8CD24. Accessed 28 May 2009

25. Kerr BM, Thummel KE, Wurden CJ et al (1994) Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10, 11-epoxide formation. Biochem Pharmacol 47:1969–1979

26. Ethell BT, Anderson GD, Burchell B (2003) The effect of valproic acid on drug and steroid glucuronidation by expressed human UDP-glucuronosyltransferases. Biochem Pharmacol 65:1441–1449

27. Miners JO, Birkett DJ (1998) Cytochrome P450 2C9: an enzyme of major importance in human drug metabolism. Br J Clin Pharmacol 45:525–538

28. Patsalos PN, Fröscher W, Pisani F, van Rijn CM (2002) The importance of drug interactions in epilepsy therapy. Epilepsia 43:365–385

29. Sabers A, Buchholt JM, Uldall P, Hansen EL (2001) Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res 47:151–154

30. Sabers A, Ohman I, Christensen J, Tomson T (2003) Oral contraceptives reduce lamotrigine plasma levels. Neurology 61:570–571

31. Tran TA, Leppik IE, Blesi K, Sathanandan ST, Remmel R (2002) Lamotrigine clearance during pregnancy. Neurology 59:251–255

32. Pennell PB, Newport DJ, Stowe ZN et al (2004) The impact of pregnancy and childbirth on the metabolism of lamotrigine. Neurology 62:292–295

33. de Haan GJ, Edelbroek P, Segers J et al (2004) Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. Neurology 63:571–573

34. Tomson T, Palm R, Källén K et al (2007) Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. Epilepsia 48:1111–1116

35. Cramer JA, Glassman M, Rienzi V (2002) The relationship between poor medication compliance and seizures. Epilepsy Behav 3:338–342

36. Handoko KB, Zwart-van Rijkom JE, Hermens WA, Souverein PC, Egberts TC (2007) Changes in medication associated with epilepsy-related hospitalisation: a case-crossover study. Pharmacoepidemiol Drug Saf 16:189–196