The Use of Generic Anti-Epileptics Drugs in Patients with Epilepsy

(updated January 2014 to incorporate relevant MHRA guidance)

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A consensus view from the:

United Kingdom Clinical Pharmacists Association (UKCPA): Neurosciences Group
&
Pharmaceutical Market Support Group (PMSG):
Generics Sub-Group

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Summary

Prescribing of generic anti-epileptic drugs (AED) for patients with epilepsy is an issue that divides opinion. The financial benefits of switching to less costly treatments are the most obvious drivers for changing patients' AEDs. Generic drug prescribing can improve medication safety because consistency in prescribing the same drug name avoids confusion of multiple brand names. There is some opposition to switching formulations of AEDs because of concerns of inequivalence between the brands and generics. There are limited published papers investigating the risks of brand to generic prescribing with a wide range of findings. The evidence appears to suggest that while many patients are likely to tolerate a switch to a generic AED which may differ slightly in pharmacokinetics there will be a small proportion of patients who are already at the threshold of tolerability of their branded AED and may find a switch to a generic drug problematic (this also applies to switches between different generic formulations). The consequences of breakthrough seizures in previously stable patients can be costly, having a deleterious effect on patients' health, independence, lifestyle and ability to drive. The Generics Sub-Group of Pharmaceutical Market Support Group have reviewed the evidence and compiled a document that provides advice on the safety and appropriateness of switching between brands and generic formulations of all AEDs. This document also incorporates the findings of the recent Medicines and Healthcare Products Regulatory Agency (MHRA) report on formulation switching of antiepileptic drugs.

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Introduction

Epilepsy

Epilepsy is a common condition with up to 50 cases of new-onset epilepsy per 100,000 people each year. (Kwan 2011) Seizures, of which there are many clinical manifestations, characterise epilepsy. The underlying cause may be neurological, neurovascular, neuroanatomical, metabolic, auto-immune or psychogenic so classifications can be controversial and misdiagnoses are common. Of those who are diagnosed with epilepsy, two-thirds are likely to become seizure-free on or off treatment (defined as no seizures in a 5-year period). Around 20-30% of epilepsy patients will develop drug-resistant epilepsy (Kwan 2011, Picot 2008, NICE CG137) often requiring multiple therapies to reduce the seizure frequency.

Use of Generic AEDs

The majority of the classic first-line therapies in epilepsy are available from multiple manufacturers as brands and generic products (phenytoin, carbamazepine, sodium valproate, phenobarbital). Some of the second generation anti-epileptic drugs (AED) have generic versions available or coming soon. The awarding of generic AED medicines contracts for secondary and tertiary care in the NHS has been problematic for some time because of concerns about the benefits versus risks of using generic AEDs to treat epilepsy.

Controversy around switching

The financial benefits of switching to less costly treatments are the most obvious drivers for changing patients' AED products. Generic drug prescribing can improve medication safety because consistency in prescribing the same drug name avoids confusion of multiple brand names. Hospital contracts change infrequently so patients would seldom be exposed to a change of manufacturer in secondary care. Many medicines licensed for the control of seizures are also used for other indications. In practice it would be difficult to manage the use of two products; a generic for non-epilepsy indications and the brand for epilepsy.

There is some opposition to switching AEDs to generic versions because of concerns of inequivalence between the brands and generics. There are limited published papers investigating the risks of brand to generic prescribing with a wide range of findings. Increase in seizure frequency has been linked to natural variation in disease, low medication compliance, infection, nutrition status, hydration status, tiredness, and stress as well as changes between products that may have bioavailability or pharmacokinetic differences. (National Society for Epilepsy 2010, Brain and Spine Foundation 2012, Sperling 2008) Existing evidence is unable to stratify these risks in order of importance. The incidence of seizure recurrence in previously seizure-free patients has been reported to be 30% with no known cause and another 10% with an identifiable cause such as omission of doses, sleep deprivation or fever. (Schiller 2009) This confounds the determination of the impact of brand to generic switching and makes recommendations problematic.

Recommendations from epilepsy groups and governing bodies

Many patient and other special-interest groups recommend prescribing certain AEDs by brand. (Epilepsy Action 2011, AAN 2006, Bialer 2010) In practice this is difficult and there is evidence that primary care epilepsy patients are switched from one generic or branded product to another without consultation more frequently than expected. (Rawnsley 2009, Wilner 2002) This may be as a result of many factors including a lack of awareness or information available to patients, carers, prescribers or community pharmacists. A survey of readers of Epilepsy Action's membership magazine 'Epilepsy Today' found that 36% of epilepsy patients who were given a different manufacturer's version of their AED refused to accept the product. The importance of shared decision-making is widely acknowledged and essential for improved adherence to medicines (DoH 2010). It is thought that 30 to 50% of medicines for long term conditions are not taken by patients as recommended (NICE CG76), and studies investigating AED adherence have demonstrated similar rates of compliance (Hovinga 2008, Ettinger 2009, Jones 2006) with some finding that non-adherent patients were significantly more likely to have seizures than adherent patients (Hovinga 2008, Jones 2006). Therefore any switching between brand and generic medicines must be in agreement with patients.

NICE (NICE CG137) has published a statement on AEDs which states:

"Consistent supply to the child, young person or adult of a particular manufacturer's AED preparation is recommended, unless the prescriber, in consultation with the child, young person, adult and their family and/or carers as appropriate, considers that this is not a concern. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side effects. Consult the summary of product characteristics (SPC) and British National Formulary on the bioavailability and pharmacokinetic profiles of individual AEDs, but note that these do not give information on comparing bioavailability of different generic preparations."

The Medicines and Healthcare Products Regulatory Agency (MHRA) has produced a report on the Recommendations of the Commission on Human Medicines (CHM) from July 2013 on formulation switching of antiepileptic drugs (MHRA July 2013). This report concerns the CHM's recommendations on issues relating to brand/generic prescribing and switching between formulations for antiepileptic drugs. The MHRA found that problems related to small differences in bioavailability of different manufacturers' products (branded, generic) are of concern for some drugs but not for some others that have a wider therapeutic index and/or high solubility and permeability. In broad terms, three groups of AEDs were identified regarding concerns of the potential risk related to switching between products:

- Category 1 – definite concerns – need specific prescribing, supply and dispensing measures to ensure consistent supply of a particular product (for treatment of epilepsy only, not for neuropathic pain or other indications). This can be a specific brand leader (originator) product, a "branded generic" (i.e.

generic approved with a brand name) or a specified manufacturer's generic product.

- Category 2 – possible concerns – according to clinicians' judgement, as per NICE guideline.
- Category 3 – unlikely to be concerns – no specific measures normally required. Acceptable to prescribe generically unless there is a reason not to (e.g. patient anxiety, risk of confusion being caused by different preparations being taken leading to dosing errors).

Bioequivalence

Generic drugs are required to be bioequivalent to the reference branded formulation. Bioequivalence tests are carried out in small samples of healthy volunteers. The European Medicine Agency (EMEA) criteria for bioequivalence requires the upper and lower limits of 90% confidence intervals (CI) for a generic drug's area under the curve (AUC) and maximum concentration (Cmax) to be within 80% to 125% of the reference branded formulation. To fit the 90% confidence interval within these limits, the generic drug and the brand drug have to be almost identical and the only theoretical exception is if the generic drug formulation has a markedly lower variability than the brand formulation. However, concern has been raised that generic AEDs which are at the outer limits of these ranges may cause problems in some patients who are switched from branded drugs or from other generic drugs at the opposite end of the range. (EMEA 2010, Peterson 2011)
The EMEA has developed tighter criteria for drugs with a narrow therapeutic index and recommend these drugs have AUC and Cmax confidence intervals within 90.00 to 111.11% however they have not requested any AEDs are tested with these limits yet. (EMEA 2010)

Biopharmaceutics Classification System (BCS)

One reference suggests that there are three pharmacokinetic properties that predispose AEDs to problems with generics: low water solubility, narrow therapeutic range, and nonlinear pharmacokinetics.

A drug is considered to have high solubility when the highest dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1 to 7.5 at 37°C. A drug is considered to be highly permeable when the extent of absorption is 90% or higher.
The drugs are then classified into four Biopharmaceutics Classification System (BCS) classes: Class I: high solubility/high permeability; Class II: low solubility/high permeability; Class III: high solubility/low permeability; Class IV: low solubility/low permeability.

The BCS classification can provide an estimate for the likelihood of problems with generic substitution not predicted by in vitro dissolution testing. (Anderson 2008)
A value for BCS is included in the individual drugs' monographs where it is known.

Evidence for and against switching AED from brand to generics.

Evidence in the literature to support or refute the practice of switching patients with epilepsy from brand AEDs to generic versions was found in the form of observational studies looking at seizure frequency after switching formulations, bioequivalence studies measuring the pharmacokinetics of AEDs, surveys of physicians, pharmacists' and patients' experiences with generic switching, data analysis studies of healthcare claims from patients in the US and Canada after generic switching and case reports of patients who have experienced problems. Switching between brand and generic AEDs has been associated with: more patients requesting to be returned to brand AED when compared to non-AED switchback rates (Andermann 2007, LeLorier Neurology 2008), greater utilisation of healthcare (Zachry 2009, Rascati 2009, Hansen 2009, Labiner 2010), increased seizure frequency in some patients and increased side-effects in others (Berg 2008, Wilner 2002, Kramer 2007). However determining that the generic switch was the cause was often suggested rather than proven and some studies have not found any problems with switching. (Czapinski 2009) Each type of research has its own limitations and none of the studies provided compelling evidence that generic AEDs are likely to cause problems in large numbers of patients nor that they are safe and suitable for all patients.

The evidence relating to specific drugs has been reported under the individual drugs' monographs. The studies discussed in this section have reviewed multiple AEDs however compliance was often under-reported and where it had been considered the criteria for inclusion in the study was often a medication adherence rate of 80%. (Erickson 2011)

Observational studies looked at seizure frequency after switching between brand and generic AEDs so assessed the drug in patients rather than healthy volunteers and were especially useful when they compared patients with a control group who had not switched. A Polish study observed 646 patients with drug-resistant epilepsy with partial seizures treated with 1–3 new generation antiepileptic agents. Switching any of these drugs to generics did not increase seizure frequency (mean seizure frequency per month before and after a switch was 6.7 vs 6.9 for lamotrigine, 8.2 vs 8.0 for gabapentin and 9.9 vs 9.6 for topiramate). The percentage of patients that needed to be switched back to the original medication was less than 2.1%. (Czapinski 2009)

The healthcare systems in the US and Canada record data on patients' claims for healthcare. Studies using this data have the advantage of being able to include large numbers of patients however much of the clinical background to the patients' circumstances is not available e.g. seizure frequency, other medical problems, medication compliance, AED blood levels, number of other AEDs used (a marker of epilepsy that is more difficult to manage). Analysis has shown associations between generic switching and an increase in adverse events, however, causation has not been proved in any of the studies reviewed. Data analysed from healthcare claims databases in the US have found that epileptic patients receiving emergency care for epilepsy related-events were more likely to have been switched between brand and

generic AEDs than epileptic patients seen in outpatients during the same period (11.3% vs 6.5% [Zachry 2009], 11% vs 6.3% [Rascati 2009], 11.1 vs 6.5% [Hansen 2009]). These studies assumed that patients experiencing a breakthrough seizure would seek emergency care. One study found increased rates of healthcare utilisation during periods of generic AED use in epileptic patients with increased use of all prescription drugs (IRR = 1.13 [95% CI 1.13–1.14]) and higher rates of hospitalisation (IRR = 1.24 [95% CI 1.19–1.30]); outpatient visits: (IRR = 1.14 [95% CI 1.13–1.16]); lengths of hospital stays: (IRR = 1.29 [95% CI 1.27–1.32]) (Labiner 2010).
Two of the studies occurred shortly after generic zonisamide introduction so over-representation of one drug may have biased results.

Two Canadian studies analysed healthcare claims data following compulsory switching policies for brand to generic lamotrigine. One study found switchback to brand rates to be 12.9% for lamotrigine, 21% for clobazam and valproic acid/divalproex compared to 1.5 – 2.9% for non-AED (SSRIS, statins). (Andermann 2007)
The second study found 28% lamotrigine patients switched back to brand, 44% clobazam, 31% gabapentin and 21% carbamazepine CR patients switching back to brand compared to 8 – 9% of non-AED users. Switchback rates may show an association with lower tolerance to the generic drug however causation cannot be proven without the full clinical details. (LeLorier Neurology 2008)

Pharmacokinetic studies have the advantage of looking at individual drugs rather than generalising all AEDs together. These studies often use healthy volunteers who may not provide a realistic comparison to the population of patients who suffer with epilepsy. Results of the analysis of AED blood levels in patients or volunteers can only be applied to the specific brands and generics used in the test and cannot be extrapolated to other generics on the market. Often studies have reviewed patients who have experienced problems after generic switching and do not provide data on patients who have successfully switched so may bias the evidence base. An AED's pharmacokinetic levels may be found to be within the accepted bioequivalence standards however this still does not answer the question about whether the EMEA's criteria for bioequivalence is acceptable for AEDs when there are opinions that seizures can occur even with small changes in plasma levels.
The bioequivalence criteria of 80% - 125% has led some to believe that generics can provide great variations in levels of AUC and Cmax and particularly when switching between generics which may be at the opposite ends of the range.

A US study analysed data that had been submitted to the FDA when approving generic AED formulations. 141 generic AED products were evaluated in 258 bioequivalence studies. AUC for generic and brand formulations were very similar with AUC differing by < 15% for 255 of 258 (98.8%). Cmax differed between generic and brand formulations by 15 – 25% in 10.85%. For generic to generic bioequivalence it was found that 83.4% of the generic pairs had an AUC that differed by <15%, (14.3% by 15 – 25%, 2.35% by > 25%). Cmax differed by <15% in 61.2, (35.1% by 15 - 25%, and 3.7% by >25%). (Krauss 2011)

A Dutch study looked at looked at bioequivalence data from submissions to the Dutch Medicines Evaluation Board for generic AEDs. After normalisation of data this study found similar AUC ratios for brand and generic topiramate and gabapentin however the Cmax ratios varied more than AUC. Comparison of the absolute AUCs and Cmax found some were outside the confidence intervals for bioequivalence criteria. However, this study found that the inter-batch variability of pharmacokinetic data for the brand drug was similar to the variability seen with the different generic formulations despite the same brands being used throughout. (Maliepaard 2011)

Surveys of physicians, pharmacists and patients often have low response rates and therefore responders may be more likely to have experienced a problem or have stronger opinions about generic drugs than those who chose not to reply. Surveys do not provide a means of proving that the generic switch was the cause and do not take into account the possibility of coincidental seizure relapse.
A survey of neurologists in the US found that 65% of responders had a patient who experienced loss of seizure control caused by a switch between brand and generic AEDs. (Berg 2008) Another survey of neurologists in the US, with a response rate of 4.7%, found 68% reported breakthrough seizures because of brand to generic switching and 56% reported increased side-effects. 32% reported breakthrough seizures caused by generic to generic switching with 27% reporting increased side effects. (Wilner 2002)

A survey of physicians in Germany, Austria and Switzerland, with a response rate of 21.6% found 49% reported problems when switching from brand to generic. Few reported problems switching between generics (31%) or generic to brand (16%). (Kramer 2007) A survey of patients and neurologists in Canada found that 17% patients thought they had switched from a brand to generic AED and 14% had experienced problems (without further details given). Neurologists scored whether their patients experienced problems after switched (1 never to 7 frequently), the median score was 2 but with no details given of the spread of scores. (Guberman 2000)

Case reports highlight potential problems and are interesting but cannot be used to determine the frequency of events because they are only individual reports and it is clear that successful outcomes are never published.

Systematic reviews

Four systematic reviews were found in the literature reviewing evidence on brand to generic switching of AEDs. All agreed that the strongest evidence available does not suggest there should be problems switching the majority of patients between brand and generic AEDs. However, they also agree that problems have been reported in practice and the current evidence base is not sufficient to recommend that all patients can be switched from brand to generic safely.

- Crawford et al recommend that it is prudent for patients, neurologists and pharmacists to be aware of the issues and to approve generic prescribing of AEDs for certain high-risk patients prior to it being instituted. (Crawford 2006)

- Desmarais et al report that clinical deterioration, adverse effects, and changes in pharmacokinetics have been described with generic substitution of several anticonvulsants. The authors conclude that generics do not always lead to the anticipated monetary savings and also raise compliance issues. This review was limited by publication bias and heterogeneity of the studies in the literature; however they concluded that there is enough concern to advise generic switching on an individual basis with close monitoring throughout the transition. (Desmarais 2011)

- Kesselheim et al carried out a systematic review and meta-analysis of trials comparing seizure outcomes from use of brand-name and generic AEDs and found no association between loss of seizure control and generic substitution for at least three types of AEDs. Observational study data suggested that brand to generic AED switching may be associated with 'switchbacks' and increased rates of health services utilisation, but these studies are limited by unmeasured confounders and other factors in their design. The authors suggest that physicians consider more intensive monitoring of high-risk patients taking AEDs when any medication change occurs, in the absence of better data, however there is little evidence-based rationale to challenge the implementation of generic substitution for AEDs in most cases. (Kesselheim 2010)

- Yamada et al found the available literature conflicting. Retrospective studies suggest a possible relationship between substitution of generic AEDs and increased utilisation of medical services or higher switchback rates. Results from the majority of small prospective studies reviewed failed to show significant differences in clinical outcomes or in pharmacokinetic parameters used to determine bioequivalence. The strongest available levels of evidence indicate that brand to generic AED substitution is generally not problematic, although there may be some groups of patients more prone to complications. Some evidence suggests that switches between generic AEDs in individual patients may result in increased utilisation of health care resources. (Yamada 2011)

The ideal type of study

Further studies are needed to provide the best evidence for making a decision on whether it is safe to switch brand AEDs to generics. There are a few studies already being undertaken in the US however it is not known when they will report their results. These include a prospective, blinded 4-period trial with rigorous pharmacokinetic methods, where people with epilepsy are randomised to receive

chronic dosing of a single generic product or the brand AED. Another study in the US is a prospective, randomised trial in people with epilepsy comparing two generic products at the extremes of bioavailability. A third type of study has been suggested that should examine the outlier patients, using rigorous pharmacokinetic methods to determine whether patients who experience unexpected adverse effects or loss of seizure control with generic switches truly have differences in AED concentrations. These studies should establish whether patients are likely to experience problems when switching between brand and generic AEDs. (Privitera 2011)

In summary

The evidence appears to suggest that while many patients are likely to tolerate a switch to a generic AED which may differ slightly in AUC and Cmax there will be a small proportion of patients who are already at the threshold of tolerability of their branded AED and may find a switch to a generic drug problematic. The consequences of breakthrough seizures in previously stable patients can be costly, having a deleterious effect on patients' health, independence, lifestyle and ability to drive.

In an attempt to provide consistency and advice across the NHS, the Generics Sub Group of PMSG set up a working group to look at whether practice could be standardised. See appendix 9 for members of the group.

Principles for switching:

- Switching should only be considered where there is a significant clinical, logistical or financial benefit from switching. Risks involved in switching AEDs should be mitigated as far as possible.
- Patients should be asked whether they have previously experienced problems when switching between brands and generics or if they have been told by their doctor that they must not switch between brands or generics.
- Patients are encouraged to be involved in their own healthcare, with decisions made in partnership with clinicians, rather than by clinicians alone. (DoH 2010) Therefore, patients should be asked their views about switching between brands and generics after being informed of the benefits and risks.
- Patients should not routinely be switched from existing medicines without their consent unless urgent treatment is needed. If there is likely to be a delay in ascertaining or acquiring the patient's usual brand or generic version then it is safer to administer an alternative brand or generic rather than to miss a dose.
- Sustained or Modified Release products present a greater risk and should not be considered generic (see specific product recommendations below).
- Patients with highly labile seizure control should not be switched to generics and should be maintained on their usual brand or generic version for their AED therapy.
- Patients with optimal seizure control (i.e. seizure-free or their seizure frequency has been markedly reduced) should not be switched to generics and should be maintained on their usual brand or generic version for their AED therapy. This of highest importance where there is a history of good seizure control and where the recurrence of a seizure could lead to socio-economic harm (e.g. loss of a driving license).
- If there has been a recent loss of seizure control and additional or alternative AEDs are to be prescribed, even where products are not recommended to be switched this is an opportunity to move to a generic version where this is considered to be appropriate.
    - Risk factors for increased seizure frequency include (but are not exclusive to): head trauma, infections such as meningitis or encephalitis, cerebrovascular accidents, medicine interactions, lack of compliance with AEDs, high alcohol intake or illicit drug use, or where previously used routes or modes of administration become unavailable or unsuitable.
    - Patients with allergies to certain excipients must only switch if it is known that the generic product does not contain those ingredients.
    - Epileptic patients on a ketogenic diet should not be switched to generic formulations unless agreed by the patient's healthcare team as different products have different carbohydrate content.
    - Non-epilepsy uses of AEDs do not generally have significant consequences following minor changes in dose so generic switching is unlikely to cause problems.

To ensure patients receive the most appropriate product, where differences exist between brands, most hospitals will stock a single product and a range of

formulations within the branded product range. The MHRA have provided guidance on which antiepileptics they consider to be safe and unsafe to switch formulations.

In Summary:

Patients identified as suitable for switching from brand to generic are those who agree to try a generic version and are taking an AED which is significantly cheaper as a generic. They must not have any contraindications to switching such as: sensitivity to small dose changes, experience of previous unsuccessful attempts to switch, sustained release preparations, good seizure control, serious consequences from a change in seizures (e.g. loss of driving license) and they must not be on a ketogenic diet or have allergies to the excipients in the generic version.

Sample table :

Name of drug		
Forms available	Chewable tablets	Strengths in range
	Liquid	Strengths in range
	Modified-release tablets	Strengths in range
	Suppositories	Strengths in range
	Tablets	Strengths in range
Brands available	Non-proprietary, brand name 1, brand name 2	
Recommendation		
These recommendations should not be used without consulting the 'principles for switching' section on page 11. Consider each formulation as well as brand. • What are the recommendations for staying with the formulation, the brand or both		
Rationale		
Evidence presented to support the recommendations above in more detail. Half life and the Biopharmaceutics Classification System (BCS) score has been included to provide pharmacokinetic properties that might predispose an AED to problems with generics. The drugs are classified into one of four BCS classes: Class I: high solubility/high permeability; Class II: low solubility/high permeability; Class III: high solubility/low permeability; Class IV: low solubility/low permeability. The BCS classification can provide an estimate for the likelihood of problems with generic substitution not predicted by in vitro dissolution testing. (Anderson 2008)		

Carbamazepine

Forms available	Chewable tablets	100mg, 200mg
	Liquid	100mg/5ml
	Modified-release tablets	200mg, 400mg
	Suppositories	125mg, 250mg
	Tablets	100mg, 200mg, 400mg
Brands available	Non-proprietary, Carbagen, Tegretol	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- The majority of Carbamazepine immediate release tablets are used in non-epileptic patients and maintenance of blood levels is not critical in these conditions.
- Modified-release preparations in general should not be routinely considered for switching.
- Suppositories are only available from a single manufacturer, but as the therapy is for short-term use substitution is permissible should a new product become available.
- MHRA Category 1 (prescribe and dispense according to specific brand, or specified manufacturer's generic - not recommended for switching).

Rationale

Half life: Carbamazepine: 25 to 65 hours initially, then 12 to 17 hours after repeated doses (3 to 5 weeks) due to autoinduction. Carbamazepine-10,11-epoxide: 6.1 hours. (Micromedex 2012)

Biopharmaceutics Classification System: II: (low solubility/high permeability). (Anderson 2008, MHRA 2013)

A literature search retrieved 16 relevant studies. There were various different types of data found including 9 bioequivalence studies, a survey of physicians' experiences in the US, 3 data analysis studies from healthcare claims databases (2x US and 1x Canadian), and 6 cases reported in 3 articles. A systematic review was also found which reported 12 additional studies not included in this review.

Due to the volume of information on carbamazepine the evidence reported below is a brief summary and more information can be found in appendix 2.

9 bioequivalence studies included 8 randomised crossover studies and 1 non-randomised study. The studies assessed between 10 and 40 patients each. All trials except one found similar AUCs, Cmax for brands and generics with no statistical differences and where reported no significant differences in side-effects or seizures. The study which did find significant differences in AUC and Cmax tested 3 generics which had already been identified as having large differences in dissolution between

the generics and the brand Tegretol. (Mayer 1999, Oles 1992, Jumao-as 1989, Meyer 1998, Yacobi 1999, Bialer Epilepsia 1998, Aldenkamp 1998, Olling 1999)

A survey of physicians in the US retrieved 7 reports about carbamazepine causing problems after brand to generic switching. The blood levels of patients who were switched to generic carbamazepine decreased by an average of 20% and for 3 patients who had blood levels after switching back to brand their levels returned to near the original baseline level. (Berg 2008)

There are 3 data analysis studies from healthcare claims databases. One US study found patients who had received emergency care for epilepsy related events were more likely to have switched from brand to generic and carbamazepine was one of the top 4 AEDs involved. Two studies, one Canadian and one US, measured switchback rates after patients had been switched from brand to generic and found high switchback rates for carbamazepine 20.8% and 31.5% respectively. (Hansen 2009, Labiner 2010, LeLorier Neurology 2008)

There are 6 case reports of patients who were taking branded carbamazepine and experienced problems after switching to generic. Two paediatric patients experienced adverse effects with generic carbamazepine and 4 adult patients suffered increased seizures after switching to generic. (Gilman 1993, Koch 1987, Sachdeo 1987)

A systematic review looking at potential problems with generic substitution of AEDs mentioned 12 additional studies that have not been appraised in detail for this monograph. The extra studies are briefly summarised in appendix 2 as they appear in the original paper. (Crawford 2006)

Clobazam

Forms available	Tablets	10mg
Brands available	Non-proprietary	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no specific data to suggest that switching causes problems in clinical practice. In these circumstances it seems reasonable to allow switching for most patients
- The effects of clobazam wear off over time. (SPC 2011)
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Clobazam: 36 to 42 hours. N-desmethylclobazam: 71 to 82 hours. (Micromedex 2011)

Biopharmaceutics Classification System: No data (Anderson 2008). MHRA consider clobazam to have a lack of reliable data on solubility and to have low permeability. BCS unclassified. (MHRA 2103)

A literature search retrieved 2 relevant studies, both of which were data analyses of healthcare claims in Canada.

A Canadian study analysed prescription drug dispensing claims paid for by the Ontario Drug Benefit (ODB) Formulary to identify patients on lamotrigine, clobazam or valproic acid / divalproex in January 2002 to March 2006. Rates of switch back to brand were determined [Lamictal, Frisium and Depakene (valproic acid; divalproex)] and these were compared with non-AED long-term therapies, antihyperlipidemics and antidepressants. There were 1483 generic clobazam patients (136 monotherapy and 1347 polytherapy 90.8%). AEDs had much higher switchback rates compared with other long-term drugs. The switchback rate for clobazam was 20.7% (valproic acid / divalproex 20.9% and lamotrigine 12.9%). The switchback rates for non-AEDs were substantially lower at 1.5–2.9%. The rate of switchback was lower for polytherapy for clobazam (19.8 vs. 27.1%) than patients on monotherapy. (Andermann 2007)

A Canadian study used medical and pharmacy claims data from Re´gie de l'Assurance Maladie du Que´bec database between April 1998 and July 2006. The study was analysing lamotrigine and compared the switch back to brand rates with those of 3 other AEDs and 3 non-AEDs. 1060 patients were on clobazam of which 995 (93.9%) were on polytherapy. 51.8 – 93.9% of patients on lamotrigine, clobazam and carbamazepine were on polytherapy. In contrast, polytherapy users represented 2.2% to 3.0% of patients for non-AED study populations (simvastatin, fosinopril,

carvedilol).
18.9% of clobazam patients switched to a generic and 44.1% switched back to brand. This compared to 45% gabapentin switched and 30.9% switched back; 72.3% carbamazepine CR switched and 20.8% switched back and lamotrigine 27.9% switched and 27.5% switched back. For non-AED 40.8 to 90.2% switched and 7.7 – 9.1% switched back. There were no results reported for the reasons for these switches or rates of seizures in clobazam patients. (LeLorier Neurology 2008)

Clonazepam

Forms available	Tablets	500mcg, 2mg
Brands available	Rivotril	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no specific data to suggest that switching causes problems in clinical practice. In these circumstances it seems reasonable to allow switching for most patients.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Clonazepam 30 to 40 hours. (Micromedex 2012)
Biopharmaceutics Classification System: II: (low solubility/high permeability). (Anderson 2008, MHRA 2013)

A literature search retrieved 2 relevant studies, both of which were data analyses of healthcare claims in the US.

A US retrospective case-control analysis identified claims from the Ingenix LabRx Database between 7/1/2006 and 12/31/2006. This time period was shortly after the introduction of generic zonisamide to the market in the US. Epileptic patients who had received emergency care for epilepsy-related events (cases) were more likely to have been switched between brand and generic AEDs (47/416, 11.3%), than epileptic patients seen in outpatients (controls) during the same period (81/1248, 6.5%). Clonazepam accounted for 12/47 cases and 15/81 controls who had switched. The majority of patients experiencing switches (70 of 128, 54.7%) across all AED matched cases and controls occurred within 2 months of the index date. Cases (n = 416) had 81% greater odds of having had an AED formulation switch [odds ratio (OR) = 1.81; 95% confidence interval (CI) = 1.25 to 2.63] relative to controls (n = 1248). There were no significant differences between groups regarding demographics or diagnosis. (Zachry 2009)

In another study in 2006 claims from a US pharmacy claims database (Thomson Healthcare MarketScan) were analysed. This was a time period shortly after the introduction of generic zonisamide. It was found that patients who had received emergency care for epilepsy-related events (cases) were more likely to have been switched between brand and generic AED (84/757, 11.1%) compared to epileptic patients who were seen in outpatients (controls) during the same period (147/2271, 6.5%). The odds of emergency treated epilepsy-related event was 1.78 (95% CI 1.35 – 2.36) for those who experienced a switch. The majority of switches in both cases and controls involved 1 of 4 AEDs, including clonazepam. The highest number of switches among cases occurred with zonisamide (n = 23), clonazepam (n =

21), and phenytoin (n = 19), whereas most switches among controls involved phenytoin (n = 41), zonisamide (n = 40), and carbamazepine (n = 19). There was no breakdown of the number of patients on clonazepam the control group and case group to determine or compare incidence. (Hansen 2009)

Eslicarbazepine

Forms available	Tablets	800mg
Brands available	Zebinix	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no generics available for eslicarbazepine. Patent expiry: 2021.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Eslicarbazepine: 20 to 24 hours; healthy subjects: 10 to 20 hours; epilepsy: 13 to 20 hours. (SPC 2012)

Biopharmaceutics Classification System: MHRA considered eslicarbazepine to have low solubility and high permeability and classified it as BCS II. (MHRA 2013)

A literature search retrieved no relevant studies.

Ethosuximide

Forms available	Capsules	250mg
	Syrup	250mg/5ml
Brands available	Non-proprietary, Emeside, Zarontin	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no specific data to suggest that switching causes problems in clinical practice. In these circumstances it seems reasonable to allow switching for most patients.
- Ethosuximide is mostly used in paediatrics.
- MHRA Category 3 (acceptable to prescribe generically, unless there is a reason not to e.g. patient anxiety or risk of confusion caused by different preparations leading to dosing errors).

Rationale

Half life: Ethosuximide adults: 60 hours; paediatrics: 30 hours; range: 25 to 60 hours. (Micromedex 2012)
Biopharmaceutics Classification System: I (high solubility/high permeability). (Anderson 2008, MHRA 2013)

A literature search retrieved no relevant studies.

Gabapentin

Forms available	Capsules	100mg, 300mg, 400mg
	Tablets	600mg, 800mg
Brands available	Non-proprietary, Neurontin	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no specific data to suggest that switching causes problems in clinical practice. In these circumstances it seems reasonable to allow switching for most patients.
- There is no consistent evidence to suggest that switching to a generic is any worse that switching within brand so switching can be sanctioned with this medicine.
- Most use of gabapentin is in neuropathic pain where dose is less critical than in epilepsy.
- MHRA Category 3 (acceptable to prescribe generically, unless there is a reason not to e.g. patient anxiety or risk of confusion caused by different preparations leading to dosing errors).

Rationale

Half life: Gabapentin adults: 5 to 7 hours; pediatrics: 4.44 hours. (Micromedex 2012)

Biopharmaceutics Classification System: III (high solubility/low permeability). (Anderson 2008) MHRA considered gabapentin to have high enough permeability to classify as BCS I. (MHRA 2013)

A literature search retrieved 7 relevant studies. There were various different types of data found including 2 studies of bioequivalence data (1x US and 1x Dutch), a survey of physicians' experiences in the US, 2 data analysis studies from healthcare claims databases in the US and 1 from Canada, and a Polish study monitoring seizure frequency after a switch to generics.

Due to the volume of information on gabapentin the evidence reported below is a brief summary and more information can be found in appendix 3.

A study reviewing bioequivalence data for generic approval in the US found Cmax for gabapentin varied more than most other AEDs between fasting and fed states of different generic products. (Krauss 2011)

A study reviewing bioequivalence data for generic approval in The Netherlands found that in the vast majority of cases the 90% CIs were within 80 – 125%. The pattern of CI variations for brand to generic switching was similar to brand / brand exchange and generic / generic exchange. (Maliepaard 2011)

A survey of physicians in the US retrieved 8 reports about gabapentin causing

problems after brand to generic switching. (Berg 2008)

Three studies used data from healthcare claims databases. A study in the US found that gabapentin patients who had received emergency treatment for epilepsy were more likely to have been switched between brand and generics prior to the incident. (Zachry 2009) An American study and a Canadian study found that gabapentin patients had high rates of switchback to brand (10.3% and 30.9% respectively). (Labiner 2010) (LeLorier Neurology 2008)

The authors of a study in Poland concluded that switching from brand to generic gabapentin did not increase seizure frequency and switchback rates to brand were low. (Czapinski 2009)

Lacosamide

Forms available	Intravenous infusion	10mg/ml (20ml)
	Syrup	(due to be withdrawn) 15mg/ml
	Tablets	50mg, 100mg, 150mg, 200mg
Brands available	Non-proprietary, Vimpat	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no specific data to suggest that switching causes problems in clinical practice. In these circumstances it seems reasonable to allow switching for most patients.
- MHRA Category 3 (acceptable to prescribe generically, unless there is a reason not to e.g. patient anxiety or risk of confusion caused by different preparations leading to dosing errors).

Rationale

Half Life: Lacosamide adults: 13 hours. (Micromedex 2012)
Biopharmaceutics Classification System: MHRA considered lacosamide to have high solubility and permeability and classified it as BCS I. (MHRA 2013)

A literature search retrieved no relevant studies.

Lamotrigine

Forms available	Dispersible tablets	5mg, 25mg, 100mg
	Tablets	25mg, 50mg, 100mg, 200mg
Brands available	Non-Proprietary, Lamictal	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There is a lot of evidence to support switching and some countries have mandatory switching programmes.
- The DoH has issued a statement which supports switching in the UK. (DoH 2005)
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Lamotrigine, adult healthy volunteers: 25.4 to 70.3 hours; adult epilepsy: 12.6 to 58.8 hours. Elderly: 31.2 hours. Paediatric: 7 to 65.8 hours. (Micromedex 2012)

Biopharmaceutics Classification System: I (high solubility/high permeability) (Anderson 2008). MHRA considered lamotrigine to have low solubility and therefore classified it as BCS II. (MHRA 2013)

A literature search retrieved 9 relevant studies. There were various different types of data found including 2 bioequivalence studies (Danish and Thai), a survey retrieving data from Canadian pharmacists and physicians, 2 data analysis studies from healthcare claims databases in Canada, another review of health claims in the US and a Polish study monitoring seizure frequency after switching to generics and 2 economic analyses in US/Canada.

Due to the volume of information on lamotrigine the evidence reported below is a brief summary and more information can be found in appendix 4.

A bioequivalence study measured lamotrigine pharmacokinetics in 9 patients, of which 8 had reported problems with brand to generic switching. In 5 patients the generics' pharmacokinetics were outside the Danish bioequivalence range for AEDs (90 – 111%) and for 3 of these patients this explained their reported symptoms. For 3 patients their generic lamotrigine was bioequivalent. (Nielsen 2008)

A randomised crossoever bioequivalence study in Thailand found that brand and generic lamotrigine were bioequivalent in healthy volunteers. (Srichaiya 2008)

A survey of pharmacists in Canada retrieved 14 adverse reaction reports from 71

pharmacies for patients switching from brand to generic lamotrigine. There were 11 reports of loss of seizure on generic lamotrigine with seizure control regained in 8 out of 10 patients who switched back to brand. The investigators also surveyed 544 neurologists of which 95 responded and reported 8 patients who had loss of seizure control because of brand to generic switching. Seizure control was regained in 7 patients after switchback to brand. (Makus 2007)

Four studies used data from healthcare claims databases. Three Canadian studies found lamotrigine patients had high switchback rates to brand (12.9%, 26.1% and 27.5%). Two of these studies were carried out by the same investigator and data is likely to overlap. All three studies found that generic lamotrigine was associated with an increased dose of lamotrigine and higher numbers of other AEDs prescribed as well as non-AEDs and also a higher utilisation of medical services. (Andermann 2007, Le Lorier Neurology 2008, LeLorier Curr Med Res Opin 2008). Two studies concluded that costs saved by switching to generic lamotrigine were outweighed by the concurrent increase in the utilisation of pharmacy and medical services on generic lamotrigine. (LeLorier Curr Med Res Opin 2008, Duh 2007).
An American study found patients switched from brand to generic lamotrigine did not experience a greater incidence of all-cause emergency department visits or hospitalisations than those who did not switch (0.97, 95% CI 0.8 – 117). (Erickson 2011)

A Polish study reviewed 284 patients on lamotrigine and found that switching to generic lamotrigine did not increase the seizure frequency. Switching several times in consequence of pharmacy substitution did not affect seizure frequency. (Czapinski 2009)

Levetiracetam

Forms available	Intravenous infusion	100mg/ml (5ml)
	Oral solution	100mg/ml
	Tablets	250mg, 500mg, 750mg, 1000mg
Brands available	Keppra, generic products (UCB, Winthrop, Desitin Arzneimittel GmbH, Helm, Lupin, Aurobindo, Sandoz, Apotex, Bluefish, Bristol, Torrent, Pfizer, Synthon)	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no specific data to suggest that switching causes problems in clinical practice. In these circumstances it seems reasonable to allow switching for most patients.
- MHRA Category 3 (acceptable to prescribe generically, unless there is a reason not to e.g. patient anxiety or risk of confusion caused by different preparations leading to dosing errors).

Rationale

Half life: Levetiracetam: 6 to 8 hours. (Micromedex 2012)
Biopharmaceutics Classification System: I (high solubility/high permeability). (Anderson 2008, MHRA 2013)

A literature search retrieved 3 relevant studies. These included a retrospective, observational study in the US investigating the rates of switchback to brand and two papers describing 8 case reports.

Due to the volume of information on levetiracetam the evidence reported below is a brief summary and more information can be found in appendix 5.

An observational study included 260 patients in the US who were prescribed generic levetiracetam after mandatory switching. 105 (42.9%) patients switched back to branded levetiracetam. The reasons for switchback included an increase in seizure frequency (n = 48, 19.6%), although 4 patients had decreased seizure frequency on generic 1.6%; ($p < 0.0001$). Adverse effects occurred in 8 patients on the generic (3.3%) including complaints of blurred vision (n = 4), headache (n = 3), depression (n = 2), memory loss (n = 2), aggression (n = 1), and mood swings (n = 1), where several of these adverse effects were experienced in conjunction with each other. An increase in seizure frequency following generic substitution was associated with polytherapy compared to monotherapy (RR 3.223; CI 1.512 – 6.880; $p < 0.05$). (Chaluvadi 2011)

Two US papers describe case reports of epilepsy patients who have had problems after switching from brand levetiracetam to generic.

The first paper reported that patients had an increase in seizure frequency after being changed from branded levetiracetam to generic and their seizure frequency returned to baseline after switching back to Keppra. The authors concluded there was 'probable causality' with generic levetiracetam. (Fitzgerald 2011)

Another US paper described 4 brain tumour patients who experienced increased seizure frequency following brand to generic switch. (Armstrong 2010)

Oxcarbazepine

Forms available	Oral solution	300mg/5ml
	Tablets	150mg, 300mg, 600mg
Brands available	Non-proprietary, Trileptal	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- The limited studies indicate a greater variability in blood levels with this agent. In these circumstances switching is not supported.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Oxcarbazepine: 2 hours. 0–monohydroxy metabolite: 9 hours. (Micromedex 2012)

Biopharmaceutics Classification System: II (low solubility/high permeability). (Anderson 2008, MHRA 2013)

A literature search retrieved 1 relevant study which was a bioequivalence analysis in the US.

A study used bioequivalence data for approved generic AED formulations in the US provided by the FDA Centre for Drug Evaluation and Research, Office of Generic Drugs. A total of 141 generic AED products were evaluated in 258 bioequivalence studies. Oxcarbazepine, probably due to low solubility, was particularly variable compared to other AEDs. Parent oxcarbazepine and its 10-monohydroxy metabolite met bioequivalence standards, but Cmax and AUC ratios for the parent compound were near acceptance limits. Pairs of generic AEDs were tested at the same doses and AUC for 6 of 21 pairs differed by 25 to 30%. Cmax for 7 of 12 (58%) oxcarbazepine bioequivalence studies differed by 15 to 25% between fasting and fed studies, a higher proportion than for other AEDs. (Krauss 2011)

Perampanel

Forms available	Tablets	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg,
Brands available	Fycompa	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no generics available for perampanel.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Perampanel 105 hours. (Micromedex 2012)

Biopharmaceutics Classification System: MHRA classified perampanel as BCS II. (MHRA 2013)

A literature search retrieved no relevant studies.

Phenobarbital

Forms available	Intravenous infusion	200mg/ml (1ml)
	Oral solution (elixir)	15mg/5ml
	Tablets	15mg, 30mg, 60mg
Brands available	Non-proprietary	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There is no brand so generic usage has been standard practice.
- MHRA Category I (prescribe and dispense according to specific brand, or specified manufacturer's generic - not recommended for switching) because of very narrow therapeutic index.

Rationale

Half life: Phenobarbital: 1.5 to 4.9 days. Infant half-life range is reported to be 59 to 400 hours following oral or intramuscular administration. A value of 40 to 70 hours has been reported for children. (Micromedex 2012)

Biopharmaceutics Classification System: I (high solubility/high permeability). (Anderson 2008). MHRA considered it safer to classify phenobarbital as BCS II because of the limited data. (MHRA 2013)

Phenytoin

Forms available	Chewable tablets	50mg
	Capsules	25mg, 50mg, 100mg, 300mg
	Oral solution	30mg/5ml
	Tablets	100mg
Brands available	Non-proprietary, Epanutin	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There is a lot of (older) data on switching with phenytoin.
- When phenytoin is used as a maintenance therapy switching should be avoided whenever possible.
- MHRA Category 1 (prescribe and dispense according to specific brand, or specified manufacturer's generic - not recommended for switching).

Rationale

Half life: Phenytoin (dose dependent): 7 to 60 hours. Mean 22 ± 9 hours. (Dollery 1999) Phenytoin chewable tablet: 14 hours. Suspension: 22 hours. (Micromedex 2012)

Biopharmaceutics Classification System: II (low solubility/high permeability) (Anderson 2008). MHRA considered phenytoin to have low permeability and classifiedit as BCS IV. (MHRA 2013)

A literature search retrieved 11 relevant studies. These included 6 bioequivalence studies, 3 data analysis studies from healthcare claims databases in the US, another review of health claims in the US and a survey of physicians' experiences in US.

Due to the volume of information on phenytoin the evidence reported below is a brief summary and more information can be found in appendix 6.

A randomised control trial measured brand (Dilantin) and generic (Phenytex) phenytoin levels in 10 patients and found that patients had higher phenytoin concentrations when on generic; however, this was tolerated in all but one patient. (Mikati 1992)

Two bioequivalence studies measuring phenytoin levels of brands and generics have produced results of questionable value because they included phenytoin formulations which have been withdrawn from the market. (Rosenbaum 1994, Soryal 1992)

A bioequivalence study in bone marrow transplant patients found the median total phenytoin value was the same for brand and generic; however, the range was greater for generics. The brand provided more consistent, predictable levels. (Stetz 2005)

A bioequivalence study measured phenytoin levels in 8 patients who had been switched from brand to generic and had experienced increased seizures. There was a 30% decrease in total and free phenytoin concentrations and all 8 patients' levels returned to similar pre-switch levels after restarting the brand. (Burkhardt 2004)

A study by Wilder et al (Wilder 2001) concluded that Mylan's generic extended phenytoin sodium was bioequivalent to the brand product under fed conditions. (Rackley 2005)

A bioequivalence study in the UK assessed 5 phenytoin formulations and concluded that changing the phenytoin preparation was unlikely to be of clinical significance. (Chen 1982)

Following a survey of physicians, investigators reviewed 50 cases and found 15 described patients on phenytoin who had increased seizure frequency after switching from brand to generic. Their blood levels of phenytoin decreased by an average 40%. (Berg 2008)

Two US studies used healthcare claims databases and found that epileptic patients who had received emergency care for epilepsy related events were more likely to have switched from brand to generic prior to the incident; including patients on phenytoin. (Zachry 2009, Hansen 2009). Conversely another US study using healthcare claims found event rates for all-cause emergency department visits and hospitalisations were similar for patients using generic and brand phenytoin. However, this study found phenytoin patients experienced higher rates of discontinuation, change in dose, or addition of second AED. (Erickson 2011)

Another study in the US reviewed healthcare claims and found a high rate of switching back to brand for epileptic patients (32.3%). (Labiner 2010)

In a US analysis of healthcare claims the authors concluded that there was no observed increase in emergency department visits or hospitalisation for seizures after switching to generic phenytoin. Despite a higher proportion of patients with a low phenytoin serum concentration in the post-switch period no increase in the proportion of patients with a seizure was identified. (Kinikar 2012)

Pregabalin

Forms available	Capsules	25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg
Brands available	Lyrica	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no generics available for pregabalin. Patent expiry: 2018.
- Most use of pregabalin is in neuropathic pain where dose is less critical than in epilepsy.
- MHRA Category 3 (acceptable to prescribe generically, unless there is a reason not to e.g. patient anxiety or risk of confusion caused by different preparations leading to dosing errors).

Rationale

Half Life: Pregabalin: 6.3 hours. (Micromedex 2012)
Biopharmaceutics Classification System: I (high solubility/high permeability). (Anderson 2008, MHRA 2013)

A literature search retrieved no relevant studies.

Primidone

Forms available	Tablets	50mg, 250mg
Brands available	Mysoline	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- Data are very limited to support any conclusions. The low solubility of primidone provides a theoretical risk and the lack of financial advantage means that switching should not be supported.
- MHRA Category 1 (prescribe and dispense according to specific brand, or specified manufacturer's generic - not recommended for switching).

Rationale

Half life: Primidone (systemic): 3 to 23 hours. Phenobarbital metabolite: 75 to 126 hours. Phenylethyl-malonamide (PEMA) active metabolite: 10 to 25 hours. (Micromedex 2011)

Biopharmaceutics Classification System: II (low solubility/high permeability). (Anderson 2008, MHRA 2013)

A literature search retrieved 2 relevant studies: a data analysis study from a US healthcare claims database and a case report.

A US study used claims data from PharMetrics Database between January 2000 and October 2007. 33625 patients were taking 1 of 5 AEDs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) and the mean observation period was 4 years. There were 1301 patients on primidone of which 843 (64.8%) were on polytherapy and 808 (62.1%) had stable epilepsy (defined as patients with ≤2 outpatient services per year on average throughout the observation period and no emergency department visits associated with epilepsy or non-febrile convulsions). 699 (65.6%) received only one generic version during the study period while 221 (20.8%) received two and 145 (13.6%) received three versions. After one year 116 (17.7%) had switched from brand to generic, of which 33 (27.6%) switched back to brand. Rates of healthcare utilisation were not reported for individual AEDs and neither were reasons for switchback. (Labiner 2010)

A case report describes a 16-year-old with seizures since birth who took primidone (Mysoline) 500 mg per day and clonazepam (Klonopin,) 4 mg per day, and her usual seizure frequency was one to two seizures per week. After a switch to generic primidone (Bolar Pharmecutial Co), there was a rise in seizure frequency within three weeks. Seizure frequency returned to baseline after switching back to Mysoline. Serum drug concentrations were not measured. 3 months later she was admitted to hospital (for feeding) and given generic primidone again. Despite a dose increase

primidone serum levels dropped and seizure frequency increased. (Wyllie 1987)

Other cases of primidone inequivalence are mentioned in the article by Wyllie et al. Full text of these reports has not been retrieved so they are described as they appear in the article by Wyllie et al. There have been two reported studies that compared primidone preparations in vivo. Borst and Lockwood studied nine epileptic patients who each took two preparations from different Canadian drug manufacturers, and Bielmann et al studied 12 epileptic patients who each took two lots of Mysoline from Ayerst Laboratories. In both studies, patients took each preparation for two weeks.
Borst and Lockwood found no significant differences in the mean serum primidone or phenobarbital concentrations with either preparation. Bielmann et al found that one of the lots of Mysoline gave significantly lower mean serum phenobarbital concentrations and also had a significantly slower in vitro dissolution time. The group data from Bielmann et al gave evidence that primidone bioavailability might vary from lot to lot, but they did not permit comparison of the two lots in specific individuals. (Wyllie 1987)

Retigabine

Forms available	Tablets 50mg, 100mg, 200mg, 300mg, 400mg
Brands available	Trobalt

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no generics available for retigabine. Patent expiry: unknown.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Retigabine: 7 to 11 hours. Elderly, prolonged by 30%. N-Acetyl Metabolite of Retigabine (NAMR): 7 to 11 hours. (Micromedex 2012).

Biopharmaceutics Classification System: MHRA classified retigabine as BCS IV. (MHRA 2013)

A literature search retrieved no relevant studies.

Rufinamide

Forms available	Tablets	100mg, 200mg, 400mg
Brands available	Inovelon	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no generics available for rufinamide. Patent expiry 2022.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Rufinamide: 6 to 10 hours. (Micromedex 2012)
Biopharmaceutics Classification System: MHRA classified rufinamide as BCS IV. (MHRA 2013)

A literature search retrieved no relevant studies.

Tiagabine

Forms available	Tablets	5mg, 10mg, 15mg
Brands available	Gabitril	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are no generics available for tiagabine although the first patents have expired. Therefore there is no specific data on switching brand tiagabine to generic.
- MHRA Category 3 (acceptable to prescribe generically, unless there is a reason not to e.g. patient anxiety or risk of confusion caused by different preparations leading to dosing errors).

Rationale

Half life: Tiagabine: 7 to 9 hours. (Micromedex 2011)
Biopharmaceutics Classification System: I (high solubility/high permeability). (Anderson 2008, MHRA 1)

A literature search retrieved no relevant studies.

Topiramate

Forms available	Capsules (sprinkle)	15mg, 25mg, 50mg
	Tablets	25mg, 50mg, 100mg, 200mg
Brands available	Non-proprietary, Topamax	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- The limited evidence would support cautious switching in most patients.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Topiramate: 21 hours (Micromedex 2012)
Biopharmaceutics Classification System: I (high solubility/high permeability) (Anderson 2008). MHRA classified topiramate as BCS III. (MHRA 2013)

A literature search retrieved 8 relevant studies. There were various different types of data found including 3 bioequivalence studies, (one Mexican, one Dutch and one of unknown origin), 2 Canadian data analysis studies using healthcare claims databases, and a Canadian economic analysis and 2 observational studies (one Russian and one Polish) which investigated seizure frequency after switching from brand to generic.

Due to the volume of information on gabapentin the evidence reported below is a brief summary and more information can be found in appendix 7.

A Mexican study comparing single-dose brand and generic topiramte in 28 healthy male volunteers did not report any adverse events by the participants. This study did not find any statistically significant differences in AUC or Cmax concentrations between generic and brand topiramate, and were within the bioequivalence limits of 0.80 – 1.25 (90% CI). (Pineyro-Lopez 2009) Another study bioequivalence study also found no significant differences in AUC or Cmax according to the recommended limits 0.80 – 1.25 (90% CI). (Saavedra 2010 - Abstract only)

A Dutch study looked at looked at bioequivalence data for 13 different 200mg generic topiramate products with approval based on 7 different bioequivalence studies each using the same brand, Topamax (Janssen-Cilag). For all topiramate generic-generic comparisons, 90% confidence intervals obtained using exposure-normalised AUC and Cmax values were within the 80–125% range. Comparison of the absolute, not-normalised AUC and Cmax, both for the generic and the brand Topamax, yielded a number of 90% confidence intervals outside the 80–125% range for bioequivalence. However, a very similar pattern of 90% confidence intervals was observed for the generic-generic and brand-brand exchange, despite the fact that the brand Topamax was identical in all studies. (Maliepaard 2011, Banishki 2009)

Two Canadian studies analysed healthcare claims from epilepsy patients treated with topiramate. The data collected in these studies appears to have some overlap because they both used data from the same database; one from January 2006 to October 2007 and the other between January 2006 and September 2008. (Paradis Neurology 2009, Duh 2009) The first study found that 15.7% of patients switched back to brand. The authors suggested that multiple-generic substitution of topiramate was associated with significantly higher rates of hospitalisation and pharmacy dispensings and increased direct medical costs. (Paradis Neurology 2009) The second study investigated the clinical and economic consequences following generic substitution of one vs multiple generics of topiramate. The authors concluded that multiple-generic substitution of topiramate was significantly associated with negative outcomes, such as hospitalisations and injuries, and increased health care costs. (Duh 2009)

A Russian study reviewed 220 epilepsy patients who lost seizure control of 1 year or more duration. Loss of seizure control in 60.4% cases was caused by a switch from brand to generic AED with 28.2% patients being switched to topiramate generics. The investigators also compared patients who switched from brand topiramate to generic with a control group who continued to receive the brand. Following a switch, remission was lost in 75.6% of patients and 51.9% needed emergency care and hospitalisation. (Rudakova 2011 - Abstract only)

A Polish study reviewed epilepsy patients who switched from a brand to generic topiramate and concluded that switching to generic did not increase seizure frequency. (Czapinski 2009)

Sodium Valproate (and salts)

Forms available	Capsules	150mg, 300mg
	Granules (sachet)	50mg, 100mg, 250mg, 500mg, 1g
	Intravenous infusion	100mg/ml (5ml)
	Modified release tablets	200mg, 300mg, 500mg,
	Oral solution (liquid, syrup)	200mg/5ml
	Tablets (crushable)	100mg
	Tablets (enteric coated)	200mg, 500mg
Brands available	Non-proprietary, Epilim, Episenta (valproic acid; Convulex, Dekapote forms excluded)	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There are a number of different salts (e.g. valproic acid and sodium valproate) which adds to confusion about switching.
- A cautious switching policy within the salt is supported by scanty evidence.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Sodium valproate: 16 hours (13 to 29 hours). Paediatrics (greater than 2 months): 7 to 13 hours. Neonates (less than 10 days): 10 to 67 hours. (Micromedex 2012)

Biopharmaceutics Classification System: Valproic acid BCS I (high solubility/high permeability). (Anderson 2008) MHRA did not consider there to be reliable solubility data available for sodium valproate and classified it as II or IV. (MHRA 2013)

A literature search retrieved 5 relevant studies. There were various different types of data found including a US bioequivalence study, 2 data analysis studies using health care claims databases (one US and one Canadian), a survey of physicians' experiences in the US and an article which describes 2 case reports in India.

Due to the volume of information on sodium valproate the evidence reported below is a brief summary and more information can be found in appendix 8.

A study reviewed bioequivalence data for generic AEDs and found generic divalproex varied more than most other AEDs in Cmax between fasting and fed states. (Krauss 2011)

A study in the US analysed data from a healthcare claims database and found patients switched from brand to generic divalproex did not have different rates of emergency care or hospitalisation, discontinuation of AED, dose change or additional AED therapy to patients who were not switched. (Erickson 2011)

A Canadian study analysed data from prescription claims and found that patients switched from brand to generic valproic acid / divalproex had a high rate of switching back to the brand Depakene (20.9%). (Andermann 2007)

A survey of physicians in the US retrieved 14 reports about valproic acid causing problems after brand to generic switching. The blood levels of those patients who were switched to generic valproic acid decreased by an average of 34%; 3 patients had blood levels after switching back to brand and levels returned to within 10% of the original baseline level. (Berg 2008

There are two case reports in India of two mentally retarded adults experiencing reduced seizures frequency and increased valproic acid levels after switching from brand to generic sodium valproate. No adverse effects were noticed. (Dhanaraj 2004)

Vigabatrin

Forms available	Powder (sachets)	500mg
	Tablets	500mg
Brands available	Sabril	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- There is no evidence base to oppose switching but there is unlikely to be any financial advantage in doing so.
- In these circumstances and given its use in refractory cases switching is not supported.
- MHRA Category 3 (acceptable to prescribe generically, unless there is a reason not to e.g. patient anxiety or risk of confusion caused by different preparations leading to dosing errors).

Rationale

Half life: Vigabatrin adults: 7 to 7.5 hours. Paediatrics: 5.7 hours. (Micromedex 2012)

Biopharmaceutics Classification System: MHRA considered vigabatrin to have high solubility and permeability and classified it as BCS I. (MHRA 2013)

A literature search retrieved no relevant studies.

Zonisamide

Forms available	Capsules	25mg, 50mg, 100mg
Brands available	Zonegran	

Recommendation

These recommendations should not be used without consulting the 'principles for switching' section on page 11.

- Zonisamide is not a theoretical high risk.
- There are no specific data to suggest that switching causes problems in clinical practice. In these circumstances it seems reasonable to allow switching for most patients.
- MHRA Category 2 (consider switching according to clinician's judgement, as per NICE guideline).

Rationale

Half life: Zonisamide adults: 63 hours in plasma; 105 hours in erythrocytes. (Micromedex 2012)
Biopharmaceutics Classification System: I (high solubility/high permeability) (Anderson 2008). MHRA considered zonisamide to have low solubility and classified it as BCS II. (MHRA 2013)

A literature search retrieved 4 relevant studies. These included 3 data analysis studies from healthcare claims databases in the US and a survey of physicians experiences in the US.

A US retrospective case-control analysis identified claims from the Ingenix LabRx Database between 7/1/2006 and 12/31/2006. This time period was shortly after the introduction of generic zonisamide to the market in the US. Epileptic patients who had received emergency care for epilepsy related events (cases) were more likely to have been switched between brand and generic AEDs (47/416, 11.3%), than epileptic patients seen in outpatients (controls) during the same period (81/1248, 6.5%). Zonisamide accounted for 28/47 cases and 40/81 controls who had switched. The majority of patients experiencing switches (70 of 128, 54.7%) across all AED matched cases and controls occurred within 2 months of the index date. Cases (n = 416) had 81% greater odds of having had an AED formulation switch [odds ratio (OR) = 1.81; 95% confidence interval (CI) = 1.25 to 2.63] relative to controls (n = 1248). There were no significant differences between groups regarding demographics or diagnosis. (Zachry 2009)

In another study in 2006 claims from a US pharmacy claims database (Thomson Healthcare MarketScan) were analysed. This was a time period shortly after the introduction of generic zonisamide. It was found that patients who had received emergency care for epilepsy-related events (cases) were more likely to have been switched between brand and generic AED (84/757, 11.1%) compared to epileptic patients who were seen in outpatients (controls) during the same period (147/2271,

6.5%). The odds of emergency treated epilepsy-related event was 1.78 (95% CI 1.35 – 2.36) for those who experienced a switch. The majority of switches in both cases and controls involved 1 of 4 AEDs, including zonisamide. The highest number of switches among cases occurred with zonisamide (n = 23), clonazepam (n = 21), and phenytoin (n = 19), whereas most switches among controls involved phenytoin (n = 41), zonisamide (n = 40), and carbamazepine (n = 19). There was no breakdown given of the number of patients on zonisamide in the case group and control group to determine or compare incidence. (Hansen 2009)

A US study used claims data from PharMetrics Database between January 2000 and October 2007. 33625 patients were taking 1 of 5 AEDs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) and the mean observation period was 4 years.
There were 1652 patients on zonisamide of which 1141 (69.1%) were on polytherapy and 662 (40.1%) had stable epilepsy (defined as patients with ≤2 outpatient services per year on average throughout the observation period and no ER visit associated with epilepsy or non-febrile convulsions).

1100 (66.6%) only used branded zonisamide, 255 (15.4%) used generic only and 297 (18%) used brand and generic. 324 (58.7%) received only one generic version during the study period while 150 (27.2%) received two and 78 (14.1%) received three versions. After one year 280 (23.4%) had switched from brand to generic, of which 32 (11.5%) switched back to brand. Rates of healthcare utilisation were not reported for individual AEDs and neither were reasons for switchback. (Labiner 2010)

A survey of physicians in the US found that 293 (65%) out of 451 neurologists who completed the online survey had a patient who experienced a loss of seizure control caused by either a switch from a brand to a generic AED or from uncontrolled switching between generic forms of an AED. 50/293 cases were chosen randomly for further review. There were 8 patients on zonisamide in the random sample, who were well-controlled on the brand AED, and who subsequently experienced a breakthrough seizure or increased seizure frequency after switching to a generic without other provoking factors. [Two patients were on a combination of two AEDs, both of which were switched to generics (unknown which AED)]. There were no blood levels available for zonisamide patients.(Berg 2008)

Appendix 1
Search Strategy

Embase

A literature search of Embase was carried out using the search terms: 'anticonvulsive agent', 'generic drug', 'carbamazepine', 'clobazam', 'clonazepam', 'eslicarbazepine', 'eslicarbazepine acetate', 'ethosuximide', 'etiracetam', 'gabapentin', 'gabapentin enacarbil', 'harkoseride', 'lacosamide', 'lamotrigine', 'levetiracetam', 'oxcarbazepine', 'perampanel', 'phenobarbital', phenytoin', 'pregabalin', 'primidone', 'rufinamide', 'tiagabine', 'topiramate', 'valproate semisodium', 'valproic acid', 'valproic acid derivative', vigabatrin', 'zonisamide'. The bibliographies of key articles obtained from the search were used to identify additional sources.

Cochrane

A search of Cochrane database was carried out using simple search terms:
anticonvulsive, anticonvulsant, anti-epileptic, generic, carbamazepine, clobazam, clonazepam, eslicarbazepine, ethosuximide, etiracetam, gabapentin, harkoseride, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproate, valproic, vigabatrin, zonisamide.

NeLM

A search of NeLM was carried out using simple search terms:
anticonvulsive , anticonvulsant, anti-epileptic, generic, carbamazepine, clobazam, clonazepam, eslicarbazepine, ethosuximide, etiracetam, gabapentin, harkoseride, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproate, valproic, vigabatrin, zonisamide.

NHS Evidence

A search of NHS Evidence was carried out using simple search terms:
anticonvulsive, anticonvulsant, anti-epileptic, generic, carbamazepine, clobazam, clonazepam, eslicarbazepine, ethosuximide, etiracetam, gabapentin, harkoseride, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproate, valproic, vigabatrin, zonisamide.

No date or language limits were applied to the literature searches, although limited availability of full-text papers in other languages precluded their use.

Appendix 2

Review of the evidence for carbamazepine

A non-blinded intra-individual bioequivalence study in Germany included 14 patients aged 18 – 52 years with focal epilepsy between May 1996 and February 1997. Patients were taking sustained release branded carbamazepine (Timonil 300 Retard) as monotherapy for uncontrolled epilepsy and were switched to generic carbamazepine sustained release (Fokalepsin 300 Retard). One patient dropped out because of ADRs with generic carbamazepine. For the remaining 13 patients: AUC was 111.5% (90% CI 105.6 – 117.8%), peak trough fluctuation (PTF) was 90.9% (90% CI 73.4 – 112.8%), Cmax was 110.1% (90% CI 100.4 – 117.0%). In 8 patients there were adverse effects such as dizziness, nausea, ataxia, diplopia and nystagmus. Bioequivalence standards at this time were 90% CI for AUC 80 – 125% and Cmax and PTF 70 – 143%. This meant that generic carbamazepine met the bioequivalence standards. In this study the follow-up period was very short and the patients already had uncontrolled epilepsy before their switch therefore seizure frequency was not measured. (Mayer 1999)

A prospective, randomised, double-blind, crossover bioequivalence study in the US compared generic (Epitol) for 90 days with brand (Tegretol) carbamazepine for 90 days in 40 epileptic patients (>13years old).

There were 20 patients in Group A who were seizure-free (between 5 months and 2 years) and 20 in group B who had refractory seizures (approx 2 per month for previous 3 months). The average Epitol to Tegretol ratio of AUCs was 1.04 (SD 0.28) in Group A and 1.05 (SD 0.13) in Group B.

The frequencies of breakthrough seizures in each group were similar between regimens. Group A had 1 patient drop out due to seizures; one patient had seizures during both arms of the study and two had seizures while on Tegretol. Two of these patients had a decrease in AUC >20%. Group B had 4 patients drop out due to seizures (2 on Epitol and 2 on Tegretol). The average seizure frequency was 0.25 on Epitol [SD 0.14] and 0.22 on Tegretol [SD 0.2]. Side-effects were similar in frequency and severity. Nine of 36 assessable patients had AUCs at steady state that varied by greater than 20%, 7 while on Epitol and 2 on Tegretol but did not have increased seizures. (Oles 1992)

A randomised, double-blind, crossover bioequivalence study was carried out in 10 male patients, aged 34 to 70 years with uncontrolled epilepsy in the US. Patients took either the brand (Tegretol, Geigy Pharmaceuticals) or a generic (Parke-Davis) for 5 weeks then crossed over to the other formulation. The mean blood level for generic carbamazepine was 9.6 (SD± 3.6); which was not significantly different from the brand 10.1 (SD± 4.0). The mean seizure frequency of patients with generic carbamazepine was 4.9 ± 9.2, which was not significantly different to the brand preparation 6.1 ± 12. There was no statistical difference in seizure frequency in the

patient population comparing the monthly average during the study and for 1 year prior to the study. Analysis of clinical side-effects, total blood count, and liver function tests showed no significant difference between the two formulations. This was a small study of 10 patients with follow-up for one month which is unlikely to be long enough to truly compare the seizure rates and adverse effects. (Jumao-as 1989)

A single-dose, crossover, bioequivalence study in the US assessed 3 generic carbamazepine products (by Inwood, Sidmak, Purepac) and Tegretol brand (by Ciba Geigy). 18 healthy subjects (15 males, 3 females), aged 22 to 35 years, randomly received a single-dose (200mg) of the four formulations of carbamazepine in different orders each separated by 21 day washout periods. There were statistically significant differences (<0.05) in plasma concentrations among the 4 products at sampling times between 0.5 and 25 hours however plasma concentrations were essentially identical among the 4 products from 49 hours to 169 hours. Mean concentrations ranged from 1.2 - 1.28 mcg/ml at 49 hours and 0.16 – 0.17 mcg/ml at 169 hours. Relatively small intersubject variabilities were observed for each of the 4 products with relative standard deviations (CVs) of 21% or less for Cmax and AUC. The upper confidence limit for Cmax for the Purepak product (126%) was slightly outside the FDA acceptance range of 80 – 125%. When the 3 generic drugs were compared, the CI for Cmax and AUC were all well within the range 80 – 125%. The mean time of maximum plasma concentration was 6 – 7 hours sooner for the generics ($p<0.001$) suggesting more rapid absorption of the 3 generic products. The authors suggested (following analysis) that when the single dose data was projected to steady state the Cmax difference between the 4 products would decrease (i.e. with multiple dosing). The authors concluded that the products were comparable. (Meyer 1998)

A single-centre, multiple-dose, randomised, open-label, 2-way crossover bioequivalence study was conducted in fasting volunteers at steady state in Canada. 28 subjects received the test (generic by Taro Pharmaceutical Industries Ltd) and reference product (Tegretol) as a 200 mg carbamazepine tablet 3 times a day for 8 days in a crossover fashion. The values for carbamazepine parameters AUC, Cmax, Cmin, and Cavg at steady state had coefficient of variations of less than 15% for the test and reference formulations and had 90% to 95% confidence intervals falling within 90% and 110%. Measures of pre-dose concentrations (Cmin) during the first and second dosing period showed average fluctuations of 1.3% and 4.8% respectively for the test product and 3.2% and 2.7% respectively for the reference product. Similar adverse events were observed in both the pre-treatment and treatment phases. The authors concluded that bioequivalence of the two carbamazepine products was confirmed. (Yacobi 1999)

One paper describes two bioequivalence studies which were used to test some new parameters for assessing the rate of absorption and bioequivalence of sustained-release carbamazepine products. Tegretol CR Divitab was used as the reference product and Teril 400 CR as the test product. The first study was a single-dose, randomised, crossover study in 30 male volunteers (non-smokers), aged 24 to 53 years, with a mean weight of 75 ± 7 kg, who received a single dose (400mg) of the

two carbamazepine brands separated by 3 weeks. The second study was a multiple dose, two-way randomised crossover bioequivalence study in 22 subjects (non-smokers), aged 18 to 55 years, who were given Tegretol CR Divitab or Teril 400 CR repeatedly (400mg bd) for two crossover period of 8 days.

In addition to the traditional bioequivalence parameters (AUC, Cmax and Tmax), the following measures were also taken: mean residence time (MRT), mean absorption time (MAT), Cmax/AUC, plateau time or POT (the time span associated with the concentrations within 25% of Cmax), tapical, and Capita, (the arithmetic mean of the POT times and concentrations within 25% of Cmax, respectively) and %Co-efficient of Variance (CV) of the steady state concentration (Css) values. These are not single-point parameters, and therefore, may provide a better assessment of the superimposability of the plasma concentration curve than do Cmax and tmax alone.

The mean values of these parameters were almost identical for both the test and reference formulations, after both the single- and multiple-dose studies.
The products were within the acceptable confidence intervals for both the single and multiple dose studies and for the new and traditional bioequivalence parameters so the authors concluded these results further substantiate the therapeutic equivalence between the two formulations. (Bialer Epilepsia 1998)

A randomised open-label, observer-blind, crossover bioequivalence study in the Netherlands compared 3 different formulations of carbamazepine (Tegretol and two generics by Pharmachemie and Pharbita). 12 epilepsy patients aged 18 – 60 years on carbamazepine as monotherapy were given one of the three formulations for 3 days then crossed over to the other formulations (baseline periods allowed patients to reach steady state). Most (9/12) patients were seizure-free during the 6 months before the trial. Three patients had between 1 seizure per 2 months to 2 seizures per month. All patients except one remained seizure-free during the study period. One patient reported two seizures during the study. Therefore the authors concluded that seizure frequency did not constitute a major interfering factor in this study.

Mean AUC for Tegretol was 87.98 mg/l; Pharbita was 92.90 mg/l; Pharmachemie was 87.52 mg/l ($p = 0.89$). Mean Cmax for Tegretol was 8.28 mg/l; Pharbita was 8.67 mg/l; Pharmachemie was 8.17 mg/l ($p = 0.90$). There were no statistically significant differences found between the three products for AUC, peak and trough concentrations (Cmax and Cmin), peak time (tmax) and range. No differences were found between the three carbamazepine formulations during the day for cognitive test scores ($p = 0.43$). The authors concluded that the three carbamazepine formulations could generally be considered equivalent. However this was a small study with short follow-up periods. (Aldenkamp 1998)

A four-way, randomised, crossover, bioequivalence study measured the rate of absorption and extent of bioavailability for 4 carbamazepine products in the Netherlands. 16 healthy volunteers, aged 20 – 38 years, took single doses of the brand Tegretol and three generic products (manufactured by Pharmachemie, Centrafarm and Pharbita) separated by 2 week wash out periods. The three generic

products were chosen because of large differences in in-vitro dissolution times compared to the brand Tegretol.

The variability in the plasma concentration–time curves after administration of the products was fairly small. However, one subject had higher plasma levels in all four cases. One subject had very low plasma levels after the Centrafarm product. The Pharmachemie product's pharmacokinetics were statistically significantly different ($p<0.05$) from the brand Tegretol. The Centrafarm product did not show any significant difference from Tegretol. The Pharbita product had similar AUC but all other pharmacokinetics were significantly different ($p<0.05$) from Tegretol. The Pharmachemie product was not bioequivalent with the reference product Tegretol. The Centrafarm and Pharbita products were equivalent with respect to the extent of absorption. For *C*max none of the products were bioequivalent with Tegretol.

The authors concluded: the qualitative differences in the in-vitro dissolution rates of the four products investigated were in the same order as the in-vivo absorption rates after administration of the products to healthy volunteers. (Olling 1999)

A survey of physicians in the US found that 293 (65%) out of 451 neurologists who completed the online survey had a patient who experienced a loss of seizure control caused by either a switch from a brand to a generic AED or from uncontrolled switching between generic forms of an AED. 50/293 cases were chosen randomly for further review. There were 7 patients on carbamazepine in the random sample, who were well-controlled on the brand AED, and who subsequently experienced a breakthrough seizure or increased seizure frequency after switching to a generic without other provoking factors. [Two patients were on a combination of two AEDs, both of which were switched to generics (unknown which AEDs)]. The blood levels of patients who were switched to generic carbamazepine decreased by an average of 20% which was less of a decline than those switched to phenytoin (40%) or valproic acid (34%). 3 patients had blood levels after switching back to brand and levels returned to near the original baseline level. (Berg 2008)

In a study in 2006 claims from a US pharmacy claims database (Thomson Healthcare MarketScan) were analysed. This was a time period shortly after the introduction of generic zonisamide. It was found that patients who had received emergency care for epilepsy-related events (cases) were more likely to have been switched between brand and generic AED (84/757, 11.1%) compared to epileptic patients who were seen in outpatients (controls) during the same period (147/2271, 6.5%). The odds of emergency treated epilepsy-related event was 1.78 (95% CI 1.35 – 2.36) for those who experienced a switch. The majority of switches in both cases and controls involved 1 of 4 AEDs, including carbamazepine. The highest number of switches among cases occurred with zonisamide (n = 23), clonazepam (n = 21), and phenytoin (n = 19) and carbamazepine had 5. The most switches among controls involved phenytoin (n = 41), zonisamide (n = 40), and carbamazepine (n = 19). There was no breakdown of the number of patients on carbamazepine in the control group and case group to determine or compare incidence. (Hansen 2009)

A US study used claims data from PharMetrics Database between January 2000 and October 2007. 33625 patients were taking 1 of 5 AEDs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) and the mean observation period was 4 years.
There were 9928 patients on carbamazepine of which 3871 (39%) were on polytherapy and 5247 (52.9%) had stable epilepsy (defined as patients with ≤2 outpatient services per year on average throughout the observation period and no emergency department visits associated with epilepsy or non-febrile convulsions). 3939 (39.7%) only used branded carbamazepine, 4770 (48%) used generic only and 1219 (12.3%) used brand and generic. 4312 (72%) received only one generic version during the study period while 1076 (18%) received two and 601 (10%) received three versions.
After one year 818 (10.3%) had switched from brand to generic, of which 283 (31.5%) switched back to brand. Rates of healthcare utilisation were not reported for individual AEDs and neither were reasons for switchback. (Labiner 2010)

A Canadian study used medical and pharmacy claims data from Re´gie de l'Assurance Maladie du Que´bec database between April 1998 and July 2006. The study was analysing lamotrigine and compared the switch back to brand rates with those of 3 other AEDs and 3 non-AEDs. There were 851 patients on carbamazepine CR, of which 441 (51.8%) were on polytherapy. More than 82.7% of patients on lamotrigine, clobazam and gabapentin were on polytherapy. In contrast, polytherapy users represented 2.2% to 3.0% of patients for non-AED study populations (simvastatin, fosinopril, carvedilol). 72.3% of the carbamazepine patients switched to generic and 20.8% switched back to brand. This compared to lamotrigine 27.9% switched and 27.5% switched back; clobazam 18.9% switched and 44.1% switched back; gabapentin 45% switched and 30.9% switched back. For non-AED 40.8 to 90.2% switched and 7.7 – 9.1% switched back. There were no results reported for the reasons for these switches or rates of seizures in carbamazepine patients. (LeLorier Neurology 2008)

One reference describes 2 case reports in the US of carbamazepine toxicity after a switch from Tegretol to Epitol generic. Both were 6 year old boys on Tegretol who had controlled seizures and who experienced adverse effects (behavioural, lethargy and slurred speech in one, and nystagmus in the other) after a switch to generic carbamazepine. One patient's symptoms resolved upon switchback to brand but recurred when rechallenged with the generic. The other patient's symptoms resolved after a dose adjustment when serum levels confirmed a raised level with generic carbamazepine from 4.6 mcg/ml trough level to 7.3 mcg/ml. (Gilman 1993)

A case report in the US described a 30-year-old woman with partial complex seizures, well-controlled on carbamazepine (Tegretol) therapy, with stable pre-dose anticonvulsant levels. Following initiation of generic (Goldline) carbamazepine therapy, increased seizure activity was noted and serum carbamazepine level was unmeasurabley low. After Tegretol was reinstated her level increased to her usual baseline after 72 hours. (Koch 1987)

A reference described 3 case reports in the US.

1) A patient with partial complex seizures was seizure-free for 9 months on phenytoin and Tegretol and had seizures within 5 days of switching to generic carbamazepine. After 6 seizures in 3 weeks he regained seizure control after switching back to Tegretol.
2) A patient with partial complex generalised tonic-clonic convulsions was seizure-free for 3 months while on Tegretol. She had breakthrough seizures on generic carbamazepine but has been seizure-free for almost a year after switching back to brand.
3) A patient with partial seizures had been seizure-free on Tegretol for a year. She had 4 seizures in 4 days after switching to generic and had a rash on her face, arms, and hands. Switchback to Tegretol cleared her rash and she has been seizure-free for 6 months. (Sachdeo 1987)

Crawford et al carried out a systematic review of studies looking at potential problems with generic substitution of AEDs. (Crawford 2006)
A systematic review mentioned 12 additional studies that have not been appraised in detail for this monograph. The extra studies are briefly summarised below as they appear in this paper:

Glende 1983
Single dose (8 volunteers)/multiple dose (5 patients): Increased rate of absorption of generic product though overall extent of absorption similar.

Neuvonen 1985
Crossover study in 9 healthy volunteers. Five carbamazepine tablets compared.
Seven-fold differences in total bioavailability. Central side effects (dizziness, ataxia) significantly more common with products showing rapid absorption.

Hartley 1990
Double blind crossover study in 23 children. Data analysed from 19 children treated with Tegretol and generic carbamazepine for 6 weeks. No significant differences in seizure control. Significantly more neurological side-effects with the generic, though no apparent differences in serum levels.

Reunanen 1992
Crossover study in 21 patients. Compared multiple dose biovailability of slow-release products. Significant differences in bioavailability (generic 11% higher than Tegretol Retard). More seizures with branded, though the difference was not significant.

Wolf 1992
Crossover study in 10 patients. Three formulations compared in patients already on carbamazepine monotherapy. Little difference in mean values of pharmacokinetic parameters, but differences between individuals. With one preparation, a patient showed reduction in seizure frequency but increased toxicity.

Meyer 1992
Crossover study in 24 healthy volunteer. Wide range of bioavailability found in three generic formulations that had been withdrawn from use because of reports of clinical failure. Compared with Tegretol, mean Cmax 61—74% in two generics and 142% in one. Mean AUC varied from 60—113% of Tegretol.

Bialer 1998
Study in healthy volunteers. Investigated criteria for assessment of bioequivalence of controlled release carbamazepine. Found rate of absorption important to assess.

Wangemann 1998
Crossover study in 21 volunteers. No differences in rate or extent of absorption of two sustained-release formulations of carabamazepine.

Pedersen 1985
Case report of 16-year old boy. Boy with partial epilepsy caused by cerebral hemi-atrophy stable on Tegretol experienced convulsions when switched to the generic.

Hartley 1991
The in-vitro dissolution profiles of two carbamazepine formulations (Tegretol and a generic carbamazepine) have been assessed and the bioavailability of carbamazepine compared in 12 epileptic children at steady state. Dissolution from the generic formulation (100 and 200mg tablets) tended to be greater than for the proprietary tablets. However, the bioavailability and pharmacokinetics of carbamazepine when assessed at steady were similar for the two formulations. It appears, therefore, that the breakthrough seizures and higher incidence of neurological side-effects observed when children were given generic carbamazepine in place of the proprietary formulation cannot be accounted for by differences in bioavailability or pharmacokinetics.

Welty 1992
Case report of two patients. Breakthrough seizures associated with drop in serum levels of carbamazepine following switch from Tegretol to generic.

Silpakit 1997.
Crossover study in 18 patients. Pharmacokinetic parameters for three generic formulations compared with Tegretol. One generic not bioequivalent (90% CI for AUC not within 80—120% of Tegretol).

Appendix 3

Review of the evidence for gabapentin

A study used bioequivalence data for approved generic AED formulations in the US provided by the FDA Centre for Drug Evaluation and Research, Office of Generic Drugs. A total of 141 generic AED products were evaluated in 258 bioequivalence studies. Gabapentin (and oxcarbazine and divalproex) had greater proportions of bioequivalence studies in which Cmax varied by 15 to 25% between fasting and fed states of different generic products, compared to other AEDs. (Krauss 2011)

A Dutch study looked at bioequivalence data in 2008 from submissions to the Dutch Medicines Evaluation Board for generic AEDs. Gabapentin has non-linear pharmacokinetics so separate bioequivalence studies for each strength were submitted for the 400, 600 and 800mg strengths in support of generic applications. In this study gabapentin generics were compared with eight 400mg, five 600mg generics, and five 800mg generics.
Interstudy comparison found mean AUCs of 25.9 to 33.8 mcg/ml and Cmax 1.00 to 1.15 mcg/ml for 400mg strength, mean AUCs of 41.3 to 47.6 mcg/ml and Cmax 1.36 to 1.58 mcg/ml for 600mg strength, and mean AUCs 37.0 to 56.9 mcg/ml and Cmax 1.28 to 1.77 mcg/ml for 800mg strength. The average of the mean AUC and Cmax of all brand arms was calculated and the study with the closest to average value was used as a reference standard. The absolute AUC and Cmax of each generic were corrected using the ratio of the reference standard vs the brand AUC and Cmax of the bioequivalence study in question. After this normalisation, the 90% confidence intervals were estimated. The mean point estimates for the AUC ratios for all evaluated 400, 600 and 800mg studies were 100.2%, 102.7%, and 100.2% respectively, and 100.6%, 103.6%, and 97.7% for the Cmax ratios respectively. In the vast majority of cases 90% confidence intervals were within the 80–125% margin for bioequivalence, except one Cmax ratio at the lower end of the 90% confidence interval of 79.03%, two Cmax ratios were at the high end of the 90% confidence interval of 125.45% and 125.75%, and one AUC ratio was at the high end of the 90% confidence interval of 127.62%. Comparison of the absolute, not-normalised AUC and Cmax 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 brand–brand exchange despite the fact that the identical brand (Neurontin) was used in all studies. (Maliepaard 2011)

A survey of physicians in the US found that 293 (65%) out of 451 neurologists who completed the online survey had a patient who experienced a loss of seizure control caused by either a switch from a brand to a generic AED or from uncontrolled switching between generic forms of an AED. 50/293 cases were chosen randomly for further review. There were 8 patients on gabapentin in the random sample, who were well-controlled on the brand AED, and who subsequently experienced a breakthrough seizure or increased seizure frequency after switching to a generic

without other provoking factors. [Two patients were on a combination of two AEDs, both of which were switched to generics (unknown which AEDs)]. There were no blood levels for patients who were switched to generic gabapentin. (Berg 2008)

A US retrospective case-control analysis identified claims from the Ingenix LabRx Database between 7/1/2006 and 12/31/2006. This time period was shortly after the introduction of generic zonisamide to the market in the US. Epileptic patients who had received emergency care for epilepsy related events (cases) were more likely to have been switched between brand and generic AEDs (47/416, 11.3%), than epileptic patients seen in outpatients (controls) during the same period (81/1248, 6.5%).
Gabapentin accounted for 10/47 cases and 22/81 controls who had switched. The majority of patients experiencing switches (70 of 128, 54.7%) across all AED matched cases and controls occurred within 2 months of the index date. Cases (n = 416) had 81% greater odds of having had an AED formulation switch [odds ratio (OR) = 1.81; 95% confidence interval (CI) = 1.25 to 2.63] relative to controls (n = 1248). There were no significant differences between groups regarding demographics or diagnosis. (Zachry 2009)

A US study used claims data from PharMetrics Database between January 2000 and October 2007. 33625 patients were taking 1 of 5 AEDs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) and the mean observation period was 4 years.
There were 4076 patients on gabapentin of which all were on monotherapy and 3368 (82.6%) had stable epilepsy (defined as patients with ≤2 outpatient services per year on average throughout the observation period and no ER visit associated with epilepsy or non-febrile convulsions). Gabapentin patients were excluded from the study if they were on polytherapy to ensure they were taking it for epilepsy. Monotherapy patients were more likely to have stable epilepsy. 2271 (55.7%) only used branded gabapentin, 1186 (29.1%) used generic only and 619 (15.2%) used brand and generic. 1320 (73.1%) received only one generic version during the study period while 299 (16.6%) received two and 186 (10.3%) received three versions. After one year 1390 (19.4%) had switched from brand to generic, of which 64 (10.4%) switched back to brand. Rates of healthcare utilisation were not reported for individual AEDs and neither were reasons for switchback. (Labiner 2010)

A Canadian study used medical and pharmacy claims data from Re´gie de l'Assurance Maladie du Que´bec database between April 1998 and July 2006. The study was analysing lamotrigine and compared the switch back to brand rates with those of 3 other AEDs and 3 non-AEDs. There were 202 patients on gabapentin, of which 168 (83.2%) were on polytherapy. Patients on lamotrigine, clobazam and carbamazepine had 51.8 – 93.9% on polytherapy. In contrast, polytherapy users represented 2.2% to 3.0% of patients for non-AED study populations (simvastatin, fosinopril, carvedilol). 45% of gabapentin patients were switched to generic and 30.9% switched back to brand. This compared to lamotrigine 27.9% switched and 27.5% switched back; clobazam 18.9% switched and 44.1% switched back; carbamazepine CR 72.3% switched and 20.8% switched back. For non-AED 40.8 to 90.2% switched and 7.7 – 9.1% switched back. There were no results reported for the reasons for these switches or rates of seizures in gabapentin patients. (LeLorier Neurology 2008)

A Polish study reviewed 646 drug-resistant epilepsy patients with partial seizures treated with 1–3 new generation AEDs. Patients were switched from a brand to generic AED. The group included 68 patients on two brand agents switched to generic drugs. There were 182 gabapentin patients, 284 on lamotrigine and 160 on topiramate. The authors concluded that switching any of these drugs to generics did not increase seizure frequency (mean seizure frequency per month before and after a switch was 8.2 vs 8.0 for gabapentin. (6.7 vs 6.9 for lamotrigine and 9.9 vs 9.6 for topiramate). The percentage of patients that needed to be switched back to the original medication was between 0 and 2.1%. (Czapinski 2009)

Appendix 4

Review of the evidence for lamotrigine

A small bioequivalence study took place in Denmark following mandatory generic substitution in April 2005. To exempt patients from mandatory substitution, the Danish Medicines Agency requests documentation of pharmacokinetic deviations. The Danish Medicines Agency bioequivalence standard for generic antiepileptic drugs is a 90% confidence interval for the average pharmacokinetic value to be within 90–111% of the reference (brand) pharmacokinetic value.

Nine patients on lamotrigine therapy took part in the study: 8 had reported problems they attributed to the generic and 1 patient was afraid of changing lamotrigine. 5 of 9 patients showed pharmacokinetic deviations beyond the limits set by the Danish Medicines Agency in at least one relevant parameter. In three of these patients the differences (Cmax +21%; Cmin -12% and Cmax -17%; Cmin -17%, AUC -16 / -12%) and were consistent with reports of consequences, i.e. seizure in a seizure-free patient, status epilepticus in another, and gait ataxia with falls, skull fracture, and epidural haematoma in the third. In two other patients the differences (AUC -13%; Cmin +16%) did not explain the complaint. In one patient co-medicated with valproic acid, changes in Cmax and tmax were consistent with a spontaneous report of transient morning ataxia, even though Cmax deviations between the lamotrigine preparations were below 10%. Of the three remaining patients for whom the preparations were fully bioequivalent, one had made no complaints but asked for a prophylactic investigation, the second had made vague and clinically unconvincing complaints, whereas the third had convincingly reported an increase in seizures. However, she had received several generic preparations, and it is possible that the generic investigated was not the one that caused the problem.

In this small group of patients, one particular generic preparation was bioequivalent in one patient, yet had a significantly higher bioavailability in another patient. These observations favour deviations being largely due to individual, currently undefined factors of absorption interacting with the formulation of the preparations.
If the usual bioequivalence range of 80–125% (with 90% confidence intervals) were applied, the deviations related to these serious complications would be considered consistent with bioequivalence. (Nielsen 2008)

A randomised, single dose, crossover, bioequivalence study in Thailand investigated the pharmacokinetic parameters between brand lamotrigine (Lamictal) and generic (Lamidus, India) in 24 healthy, Thai, male volunteers. Each volunteer received a single dose of 100mg lamotrigine then after two weeks the second 100mg lamotrigine.

The mean AUC_{0-t} for the generic was 67.1 mcg/ml (SD 13.2) (%CV 19.6) compared to 66.4 mcg/ml (SD 14.6) (%CV 22) for the brand. The mean $AUC_{0-\infty}$ for the generic was 74.9 mcg/ml (SD 18.3) (%CV 24.4) compared to 74.3 mcg/ml (SD 20.5) (%CV 27.6) for

the brand. The mean Cmax for the generic was 1.7 mcg/ml (SD 0.3) (%CV 17.3) compared to 1.7 mcg/ml (SD 0.3) (%CV 17.8) for the brand. The mean Tmax for the generic was 1.2 mcg/ml (SD 0.9) (%CV 75.3) compared to 1.4 mcg/ml (SD 1.0)(CV 71.6) for the brand. The mean half life for the generic was 35 mcg/ml (SD 7.6)(%CV 21.7) compared to 34.7mcg/ml (SD 7.6)(%CV 22.0) for the brand.

The study participants were healthy volunteers under test conditions (wrt meals, water intake, dosing sat upright, body size, age, lack of medical conditions etc). The AUC and Cmax found no significant difference between the generic and brand lamotrigine and the authors concluded they were bioequivalent. (Srichaiya 2008)

A Canadian study survey of pharmacists took place in Ontario where there is mandatory switching between brand and generic lamotrigine and patients can only be switched back to brand if an adverse-reaction form is completed by their physician. The investigators retrieved 14 adverse-reactions forms (from 71 pharmacies) for patients switched back to brand between January 2003 and December 2004. In 11 (79%) cases there was loss of seizure control while on generic lamotrigine and in 8/10 cases seizure control was recovered after branded lamotrigine was reinstated. In 1 case, anxiety, mood swings and dizziness were cited as additional reasons.

The investigators also surveyed 544 neurologists and primary care doctors across Canada with a 17% response rate. They found that 5 (5%) of 95 respondents had filed an adverse-reaction form in the previous 12 months to specify that a patient be dispensed branded lamotrigine (not all states in Canada require these forms). Six physicians provided outcomes for 9 patients and the range of generic use of lamotrigine was 3 to 224 days. In 7 patients lamotrigine was part of polytherapy AED. In 8 patients, loss of seizure control was recorded as the reason for switching back to branded lamotrigine, and 7 of these regained seizure control with switchback to brand. The remaining patient experienced an adverse effect (“high” feeling). (Makus 2007)

A Canadian study analysed prescription drug dispensing claims paid for by the Ontario Drug Benefit (ODB) Formulary to identify patients on lamotrigine, clobazam or valproic acid / divalproex in January 2002 to March 2006. Rates of switch back to brand were determined [Lamictal, Frisium and Depakene (VPA; divalproex)] and these were compared with non-AED long-term therapies, antihyperlipidemics and antidepressants. There were 1354 generic lamotrigine patients (403 monotherapy and 951 polytherapy). AEDs had much higher switchback rates compared with other long-term drugs. The switchback rate for lamotrigine was 12.9% (11.7% in the monotherapy group and 13.4% in the polytherapy group). Switchback rates for valproic acid / divalproex were 20.9% and clobazam 20.7%. The switchback rates for non-AEDs were substantially lower at 1.5–2.9%. The lack of medical claims data prevented the identification of epilepsy as the indication for the lamotrigine, other AEDs and also any confounding comorbid conditions. (Andermann 2007)

A Canadian study used medical and pharmacy claims data from Re´gie de l'Assurance Maladie du Que´bec database between April 1998 and July 2006. Switchback rates were calculated for patients returning to brand after using generic drugs for lamotrigine compared to other AEDs (clobazam, carbamazepine CR, gabapentin) and non-AED chronic medications (carvedilol, fosinopril, simvastatin). Medical resource utilisation was compared between periods of branded vs generic use of lamotrigine.
187 (27.9%) of 671 patients treated with branded lamotrigine were switched to a generic, and 51 of these patients (27.5%) switched back to the brand. Rates of switchback were from 20.8% to 44.1% for the other AEDs and from 7.7% to 9.1% for non-AEDs. 555 (82.5%) of lamotrigine patients were on polytherapy compared to 52.8 – 93.9% for other AEDs and 2.2 – 3% for non-AEDs.
Relative to the branded lamotrigine use period, generic lamotrigine use period was associated with: a 5.1% increase in mean daily dose of lamotrigine (239.1 vs 251.4 mg; $p = 0.0149$); a higher number of dispensations for other AEDs (20.4 vs 23.9 dispensations per person-year; $p < 0.001$), as well as non-AED drugs (26.4 vs 32.8 dispensations per person-year; $p < 0.0001$); a higher utilisation rate of medical services (8.7 vs 9.8 visits per person-year; $p < 0.0001$) Rates of hospitalisation was not significantly different however longer hospital length of stay (3.29 days vs 4.86 days per person-year; $p < 0.0001$) was associated with generic lamotrigine. Outpatient visits were more frequent during the generic period compared to the brand periods (9.25 vs 8.24 visits per person per year $p < 0.0001$).

Que´bec has greater permissiveness in allowing individuals to switch between brand and generic medications compared to Ontario, where generic substitution is compulsory, and a letter of medical necessity is required for patients to switch back to brand from generic product. (LeLorier Neurology 2008)

A large US retrospective cohort analysis used pharmacy and medical claims and enrolment data from a claims database (Medicare) between 2002 and 2008. Epileptic patients taking divalproex, lamotrigine and phenytoin were studied and divided into cohorts of patients who switched from the brand to a generic version and patients who remained on the same brand AED. Inclusion in the study required > 80% adherence. Each lamotrigine cohort had 995 patients (after matching 1:1). The majority of lamotrigine patients in the study had utilised only one AED during the 6-month pre-index period. However, a significant portion (31.1 – 34.9%) utilised two AEDs and 8.6 – 10.9% utilised three AEDs and 1.9 – 2.1% utilised four AEDs or more. The incident rate (IRR) for: discontinuation of AED, dose change of AED, or AED add-on therapy per person-year was 1.00 (95% CI 0.84–1.19) for lamotrigine and 1.85 (95% CI 1.50–2.29) for phenytoin, and 1.02 (95% CI 0.88–1.42) for divalproex. The event rates of all-cause emergency department visits and hospitalisations per person-year comparing the generic switch cohort with the nonswitch cohort was 0.97 (95% CI 0.80 - 1.17) for lamotrigine, 0.96 (95% CI 0.80 - 1.16) for phenytoin, and 0.84 (95% CI 0.66 -1.06) for divalproex.

The authors concluded that patients, who switched from branded to generic lamotrigine, did not experience a greater incidence of all-cause emergency department visits or hospitalisations. They did not discontinue the formulation,

change the dosage, or augment therapy with another AED at a greater incidence than those who did not switch. (Erickson 2011)

A Polish study reviewed 646 drug-resistant epilepsy patients with partial seizures treated with 1–3 new generation AEDs. Patients were switched from a brand to generic AED. The group included 68 patients on two brand agents switched to generic drugs. There were 182 gabapentin patients, 284 on lamotrigine and 160 on topiramate. The authors concluded that switching any of these drugs to generics did not increase seizure frequency (mean seizure frequency per month before and after a switch was 6.7 vs 6.9 for lamotrigine (8.2 vs 8.0 for gabapentin and 9.9 vs 9.6 for topiramate). The percentage of patients that needed to be switched back to the original medication was 0 - 2.1%. In the lamotrigine group, even switching the drug several times in consequence of pharmacy substitution did not affect seizure frequency. (Czapinski 2009)

A retrospective open-cohort study observed periods of branded versus generic lamotrigine use by analysing health claims from Québec's health plan Régie de l'assurance maladie du Québec (RAMQ) between 08/2002 and 07/2006. Data was collected on 671 epilepsy patients during 1650.9 and 291.2 person-years of branded and generic use of lamotrigine, respectively (a combined average of 1098 days). The mean duration of observation per patient was 3 years. 222 patients switched to generic lamotrigine and 58 switched back to brand during the study period. The average daily dose of generic lamotrigine was significantly higher than during the brand period (236.9 vs. 251.4 mg; RR = 1.06; $p < 0.001$). Compared to periods of branded lamotrigine use, patients treated with generic lamotrigine received a higher number of dispensations for other AEDs (20.4 vs. 23.9 dispensations per person-year; adjusted RR = 1.17; $p < 0.001$) as well as non-AED drugs (26.4 vs. 32.8 dispensations per person-year; adjusted RR = 1.28; $p < 0.001$). A higher utilisation rate of medical services (8.73 vs. 9.81 visits per person-year; adjusted RR = 1.13; $p < 0.001$), and a longer hospital length of stay (3.29 days vs. 4.86 days per person-year; adjusted RR = 1.49; $p < 0.001$) were also observed during the generic use period versus the brand use period.

The generic-use period was associated with an increase in overall costs (2006 constant Canadian dollars) relative to brand use (C$7902 vs. C$6419/ person-year; cost ratio (CR) = 1.22; $p = 0.05$), despite the lower cost of generic lamotrigine. Costs saved by switching to generic lamotrigine were outweighed by the concurrent increase in the utilisation of pharmacy and medical services on generic lamotrigine. These costs do not reflect the acquisition costs of lamotrigine or healthcare costs in the UK. (LeLorier Curr Med Res Opin 2008)

A Canadian study investigated the economic consequences of generic substitution of lamotrigine by analysing data on patients from a public pharmacy claims database (Ontario Drug Benefit Formulary) between July 2002 and March 2006. (See Andermann 2007). 1142 patients were included in the study with median age 37 years and 53.2% females. About 13% of patients (N = 149) in the study population switched back to the brand product following generic entry while approximately 55%

(N = 623) experienced a lamotrigine dosage adjustment during the generic period. Following generic substitution, patients were observed for an average of 776 days, or 2.1 years.

Overall average monthly per-patient drug costs were $186.46 in the brand period and fell by $11.98 (6.4%) to $174.48 during generic use. Lamotrigine costs did not reduce as much as expected because of increased dosages, offsetting some of the cost savings from lower per-unit costs. During generic lamotrigine use there was increased utilisation of other AEDs $6.29 (18.5%) and non-AEDS $11.64 (25.1%). The lack of medical claims data prevents the identification of epilepsy as the indication for the lamotrigine and also any confounding comorbid conditions. It is possible that some of the observed increases in drug utilisation during the generic period were a result of natural disease progression, aging, or refractory effects of AEDs rather than deleterious effects of generic lamotrigine. These costs do not reflect the acquisition costs of lamotrigine or healthcare costs in the UK. (Duh 2007)

Appendix 5

Review of the evidence for levetiracetam

Further details of the case reports of patients experiencing problems after switching from brand to generic levetiracetam.

Two US papers describe case reports of epilepsy patients who have had problems after switching from brand levetiracetam to generic.

The first paper reported that patients had an increase in seizure frequency after being changed from branded levetiracetam to generic and their seizure frequency returned to baseline after switching back to Keppra. The authors concluded there was 'probable causality' with generic levetiracetam.

A 21 year-old male on Keppra for generalised seizures had increased seizure frequency 5 days after switching to generic. Seizure frequency reduced after switching back to brand. Pregabalin had been discontinued within a month of the switch however the authors concluded that the events were probably related to the levetiracetam switch.

A 27-year-old female was taking Keppra as part of polytherapy for refractory nocturnal complex partial seizures and secondary generalized seizures. Her seizure frequency increased after a brand to generic switch and returned to baseline control after switching back to brand.

A 48-year-old male on Keppra and lamotrigine for refractory complex partial seizures which he usually experienced in clusters (2 per month) but often with intermittent seizure-free months. The patient had increased incidence of breakthrough seizures (2 – 5 per month) and one episode of 5 seizures in 1 week, while on generic which returned to baseline (1 seizure per month) after switching back to brand.

An 81-year-old woman on Keppra for complex partial seizures had seizures occurring once every few months. Her seizure frequency increased to weekly seizures within 3 weeks after the switch to generic. No levetiracetam levels were available. (Fitzgerald 2011)

Another US paper described 4 brain tumour patients who experienced increased seizure frequency following brand to generic switch.

A 31 year old male on Keppra was switched to generic levetiracetam and three days later experienced a complex partial seizure. He was switched back to Keppra and was been seizure-free for at least 6 months with stable dose.

A 52 year old male on Keppra had a generalised seizure 4 days after switching to a generic levetiracetam. He had been seizure-free and after switching back to brand

the patient remained both seizure-free and without evidence of tumour progression for at least 7 months.

A 31 year old male on Keppra was seizure-free for 10 months. Three months after switching to generic levetiracetam he experienced two transient episodes of numbness in two fingers and his lip and slurred speech. Levetiracetam dose was increased and he remained seizure-free and without evidence of disease progression for 5 months.

A 30 year old female on Keppra prior to surgery was switched to generic a few weeks later. One week after switching she experienced intermittent focal seizure activity. After switching back to Keppra she was seizure-free and without disease progression for at least 2 months. (Armstrong 2010)

Appendix 6

Review of the evidence for phenytoin

A 6-month, double-blind, randomised, crossover study compared two extended-release phenytoin preparations: a generic (Phenytex) and a brand (Dilantin). Each patient randomly received one preparation, and then switched to the other after 3 months. 10 patients completed the study. One patient had toxic signs before they reached steady state. The remaining 9 patients had a significantly higher average (22.6%) free phenytoin concentrations during generic therapy and the total phenytoin concentration was 19.3% higher but did not reach significance. The incidence of adverse experiences was not statistically different between the two formulations. One patient had a phenytoin level of 20.5 mcg/ml on brand phenytoin which increased to 30.2 mcg/ml after 12 days on generic phenytoin. She experienced adverse effects and had her phenytoin dose reduced. 8 of the 10 patients were seizure-free throughout the study and the seizures in 2 patients were not thought to be attributable to the generic switch.

The potency of the brand lot was 99.21% ± 1.47, and the generic preparation was 104.63% ± 3.72. Phenytoin has non-linear Michaelis-Menten pharmacokinetics so a difference of 5.4% in the amount absorbed can account for a 20% difference in serum concentrations. The authors concluded that there may be increased bioavailability of generic vs brand however it was tolerated in 9 of 10 patients. (Mikati 1992)

A bioequivalence study measured phenytoin levels following the recall of a brand of phenytoin. In 1987, the Veterans Administration (VA) hospital pharmacies changed from Dilantin (Parke Davis brand) extended release phenytoin to a generic phenytoin preparation by Sidmak Laboratories. In December 1987, Sidmak recalled their phenytoin after "some batches failed dissolution specification". 116 patients receiving generic phenytoin had levels available while on the generic and then again after switching back to the brand (timing of levels in relation to dose was random). Serum phenytoin levels were 22-31% lower during the period of generic intake as compared with levels in the same patients receiving Dilantin. The usefulness of this study is questionable because the generic product they were testing had already been recalled because of dissolution problems which may be the cause of the difference in bioavailability. (Rosenbaum 1994)

A single-blind, crossover study in the UK assessed the bioavailability of 7 formulations of phenytoin. 14 epilepsy patients taking phenytoin regularly as part of their drug therapy completed the study which consisted of 4 week treatment periods on each drug. For comparative purposes, Epanutin capsules were taken as 100% bioavailable and the relative bioavailability of the other formulations was calculated. No significant differences were found between Epanutin capsules and other generic formulations. However significant differences were noted between the generic products. Phenytoin BP tablets manufactured by Regent Laboratories (now

withdrawn) had a relative bioavailability of only 76% compared with tablets manufactured by A H Cox and Company. Epanutin Infatabs differed significantly from four of the generic formulations (Evans, APS, Kerfoot, and Regent). The formulation with the lowest Cmax differed significantly from the two formulations with the highest Cmax. No statistically significant differences were found when comparing the incidence of side effects and seizure frequency for the 7 treatments.

The short duration of treatment on each drug (weeks) means that it was unlikely to reveal any clinical differences e.g. seizure control, adverse effects. The usefulness of this study is questionable as Regent phenytoin has been withdrawn and Infatabs are recognised as having a greater content of phenytoin, because it is the acid form rather than the sodium salt, and the author's conclusions are influenced by these two products. Differences between the other (non-Regent) generic formulations studied would be smaller and less likely to have clinical consequences. (Soryal 1992)

A small bioequivalence study of phenytoin in bone marrow transplant (BMT) patients was carried out following reports of problems in these patients. 19 consecutive BMT patients were identified who received phenytoin for busulfan seizure prophylaxis, and confirmed whether their prescriptions were Dilantin brand (6 patients) or Mylan generic (13 patients). The median total phenytoin value the morning after the loading dose was the same, 11 mg/dL, for both brand and generic, however the range was greater for the generic (5.5–14.5 mg/dL) than the brand (9.3–13.6 mg/dL). The brand product seemed to deliver more consistent, predictable levels reducing the need for additional doses of phenytoin. (Stetz 2005)

A small bioequivalence study in the US assessed 11 epilepsy patients, over a 5-month period, who had experienced increased seizures requiring hospitalisation, emergency room visits, or urgent clinic visits. All but one patient had a generic substituted for Dilantin. 8 patients had one or more phenytoin concentrations measured at steady-state prior to the switch to generic, while taking a generic, and after the switch back to brand. The 8 patients had no changes in daily dose of phenytoin or concomitant AEDs. Switching from brand to generic resulted in a significant 30% decrease in both total and free phenytoin concentrations. Mean total phenytoin levels were 17.7 mg/L (± 5.3) with the brand (pre-substitution), 12.5 mg/L (±2.7) on the generic, then 17.8mg/L (±3.9) on the brand (post-substitution). All 8 patients' free phenytoin levels returned to similar pre-switch levels after restarting on the brand. (Burkhardt 2004)

A comment by Rackley criticised the Burkhardt 2004 study as being too small to make conclusions about interchangeability of phenytoin brands. The author claimed a study by Wilder et al (Wilder 2001) concluded that Mylan's generic extended phenytoin sodium was bioequivalent to the brand product under fed conditions. (Rackley 2005)

A multiple-dose, crossover, bioequivalence study in the UK compared the serum phenytoin concentrations when epileptic patients took Epanutin capsules and four formulations of phenytoin sodium tablets B.P. The 5 formulations were Epanutin

capsules by Parke-Davis and generic phenytoin by Boots, Cox, Kerfoot and Macarthy. 18 patients aged 26-68 years from an epilepsy centre completed the trial. All were on long-term treatment with phenytoin alone or with other AEDs. The doses of all the drugs were kept constant throughout the course of the study. During the base-line period the patients received their usual brand of phenytoin, Boots BP tablets. Patients were changed every 3 weeks to one of the five test phenytoin preparations. Compliance was checked with tablet counts.

The mean serum phenytoin concentrations were between 39.2 and 45.9 micromol/L and ranges were between 8.0 and 104 micromol/L for the 5 formulations. Two different lots of Boots BP tablets were used in the study and a significant rise in serum phenytoin occurred when patients switched to a different batch of the brand. This could be due to a difference in bioavailability or improvements in compliance after entry to the study as there were no baseline compliance checks. The authors concluded that changing phenytoin preparation was unlikely to be of clinical significance. However, this study took place over 30 years ago and it is unknown if there was any change in adverse event rate. (Chen 1982)

A survey of physicians in the US found that 293 (65%) out of 451 neurologists who completed the online survey had a patient who experienced a loss of seizure control caused by either a switch from a brand to a generic AED or from uncontrolled switching between generic forms of an AED. 50/293 cases were chosen randomly for further review. There were 15 patients on phenytoin in the random sample, who were well-controlled on the brand AED, and who subsequently experienced a breakthrough seizure or increased seizure frequency after switching to a generic without other provoking factors. [Two patients were on a combination of two AEDs, both of which were switched to generics (unknown which AEDs)].
The blood levels of patients who were switched to generic phenytoin decreased by an average of 40% which was more of a decline than those switched to generic carbamazepine 20% or valproic acid 34%. 5 patients had blood levels after switching back to brand and levels returned to near the original baseline level. (Berg 2008)

A US retrospective case-control analysis identified claims from the Ingenix LabRx Database between 7/1/2006 and 12/31/2006. This time period was shortly after the introduction of generic zonisamide to the market in the US. Epileptic patients who had received emergency care for epilepsy related events (cases) were more likely to have been switched between brand and generic AEDs (47/416, 11.3%), than epileptic patients seen in outpatients (controls) during the same period (81/1248, 6.5%). Phenytoin accounted for 9/47 cases and 40/81 controls who had switched. The majority of patients experiencing switches (70 of 128, 54.7%) across all AED matched cases and controls occurred within 2 months of the index date. Cases (n = 416) had 81% greater odds of having had an AED formulation switch [odds ratio (OR) = 1.81; 95% confidence interval (CI) = 1.25 to 2.63] relative to controls (n = 1248). There were no significant differences between groups regarding demographics or diagnosis. (Zachry 2009)

In a study in 2006 claims from a US pharmacy claims database (Thomson Healthcare MarketScan) were analysed. This was a time period shortly after the introduction of generic zonisamide. It was found that patients who had received emergency care for epilepsy related events (cases) were more likely to have been switched between brand and generic AED (84/757, 11.1%) compared to epileptic patients who were seen in outpatients (controls) during the same period (147/2271, 6.5%). The odds of emergency treated epilepsy-related event was 1.78 (95% CI 1.35 – 2.36) for those who experienced a switch. The majority of switches in both cases and controls involved 1 of 4 AEDs, including phenytoin. The highest number of switches among cases occurred with zonisamide (n = 23), clonazepam (n = 21), and phenytoin (n = 19), whereas most switches among controls involved phenytoin (n = 41), zonisamide (n = 40), and carbamazepine (n = 19). There was no breakdown of the number of patients on phenytoin in the control group and case group to determine or compare incidence. (Hansen 2009)

A US study used claims data from PharMetrics Database between January 2000 and October 2007. 33625 patients were taking 1 of 5 AEDs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) and the mean observation period was 4 years.
There were 16668 patients on phenytoin of which 5873 (35.2%) were on polytherapy and 8040 (48.2%) had stable epilepsy (defined as patients with ≤2 outpatient services per year on average throughout the observation period and no emergency department visits associated with epilepsy or non-febrile convulsions).

7560 (45.4%) only used branded phenytoin, 5689 (34.1%) used generic only and 3419 (20.5%) used brand and generic. 8488 (93.2%) received only one generic version during the study period while 462 (5.1%) received two and 158 (1.7%) received three versions. After one year 2259 (12.1%) had switched from brand to generic, of which 760 (32.3%) switched back to brand. Rates of healthcare utilisation were not reported for individual AEDs and neither were reasons for switchback. (Labiner 2010)

A large US retrospective cohort analysis used pharmacy and medical claims and enrolment data from a claims database (Medicare) between 2002 and 2008. Epileptic patients taking divalproex, lamotrigine and phenytoin were studied and divided into cohorts of patients who switched from the brand to a generic version and patients who remained on the same brand AED. Inclusion in the study required > 80% adherence. Each phenytoin cohort had 745 patients (after matching 1:1). The majority of phenytoin patients in the study had utilised only one AED during the 6-month pre-index period. However, a significant portion (28.5 – 28.6%) utilised two AEDs and 5.9 – 6.4% utilised three AEDs and less than 1% utilised four AEDs or more.

The incident rate for: discontinuation of AED, dose change of AED, or AED add-on therapy per person-year was 1.85 (95% CI 1.50–2.29) for phenytoin, 1.00 (95% CI 0.84–1.19) for lamotrigine and 1.02 (95% CI 0.88–1.42) for divalproex.
The event rates of all-cause emergency department visits and hospitalisations per person-year comparing the generic switch cohort with the non-switch cohort was

0.96 (95% CI 0.80 -1.16) for phenytoin, 0.97 (95% CI 0.80 - 1.17) for lamotrigine, and 0.84 (95% CI 0.66 -1.06) for divalproex.

The authors concluded that patients, who switched from branded to generic phenytoin, did not experience a greater incidence of all-cause emergency department visits or hospitalisations. However they also found phenytoin patients experienced higher rates of discontinuation, change in dose, or addition of second AED. (Erickson 2011)

A retrospective US study analysed claims between July 2007 and May 2008 from a pharmacy and medical database (Kaiser Permanente Colorado). 222 patients were switched from brand (Dilantin Kapseals) to a generic phenytoin (manufactured by Taro Pharmaceuticals) and data included 6 months prior and 6 months post-switch for each patient. 24 (10.8%) and 16 (7.2%) patients had their phenytoin dose increased in the pre- and post-switch periods respectively ($p > 0.05$); 16 (7.2%) and 13 (5.9%) patients had their phenytoin dose decreased in the pre- and post-switch periods, respectively ($p > 0.05$). 14 patients (6.3%) in each time period (pre- and post- switch) had seizure events in resulting in emergency department visits or hospitalisation ($p = 1.00$) of which 3 (1.4%) patients experienced a seizure event in both time periods. A total of 129 (58.1%) and 199 (89.6%) patients had at least 1 phenytoin serum concentration measured in the pre-switch and post-switch periods, respectively. Toxic serum concentrations (20 – 30 mcg/ml) with symptom events were not significantly different between the study periods 26 [11.7%] pre-switch vs 27 [12.1%] post-switch, $p >0.05$. More patients in the post-switch period had ≥ 1 low serum concentration than in the pre-switch period 96 [43.2%] vs 50 [22.5%] ($p < 0.001$). 6 (12.0%) patients in the pre-switch period and 6 (6.3%) patients in the post-switch period who had a low serum concentration experienced a seizure event that resulted in an emergency department visit or hospitalisation.

The authors concluded that there was no observed increase in emergency department visits or hospitalisation for seizure after switching to generic phenytoin. Despite a higher proportion of patients with a low phenytoin serum concentration in the post-switch period no increase in the proportion of patients with a seizure was identified. There was a low prevalence of seizures in this study so a larger study would be needed to confirm this effect. (Kinikar 2012)

Appendix 7

Review of the evidence for topiramate

In a Mexican study, 28 healthy male volunteers were given a single low-dose (100mg) of a brand or a generic topiramate and then a single dose of the alternative drug 3 weeks later. The mean Cmax with the generic formulation was 1.914 (± 0.429) mcg/ml, and the Tmax was 1.776 (± 1.305) hours. With the brand, the mean Cmax was 1.908 (± 0.648) mcg/ml and 2.0 (± 1.669) hours. The t½ values with the generic and brand formulations were 26.22 (± 5.96) and 27.21 (± 7.53) hours, respectively. The mean relative bioavailabilities (generic / reference) for Cmax, AUC^{0-t}, and AUC^{0-oo}, were 1.08, 1.02, and 1.08, respectively. No adverse events were reported by the participants. This study did not find any statistically significant differences in AUC or Cmax concentrations between generic and brand topiramate, and were within the bioequivalence limits of 0.80 – 1.25 (90% CI). (Pineyro-Lopez 2009)

A Dutch study looked at looked at bioequivalence data in 2008 from submissions to the Dutch Medicines Evaluation Board for generic AEDs. There were 13 different 200mg generic topiramate products with approval based on 7 different bioequivalence studies each using the same brand, Topamax (Janssen-Cilag). Interstudy comparison of topiramate found mean AUCs from 125.3 to 158.6 mcg/ml, and Cmax from 4.17 to 5.05 mcg/ml. The average of the mean AUC and Cmax of all brand arms was calculated and the study with the closest to average value was used as a reference standard. The absolute AUC and Cmax of each generic were corrected using the ratio of the reference standard vs the brand AUC and Cmax of the bioequivalence study in question. After this normalisation, the 90% confidence intervals were estimated. For all the bioequivalence studies the mean point estimate for the AUC ratio was 101.16%, and 99.55% for the Cmax ratio. For all topiramate generic-generic comparisons, 90% confidence intervals obtained using exposure-normalised AUC and Cmax values were within the 80–125% range.

Comparison of the absolute, not-normalised AUC and Cmax, both for the generic and the brand Topamax, yielded a number of 90% confidence intervals outside the 80–125% range for bioequivalence. However, a very similar pattern of 90% confidence intervals was observed for the generic-generic and brand-brand exchange, despite the fact that the brand Topamax was identical in all studies.
(Maliepaard 2011, Banishki 2009)

The third study (abstract only reviewed) used very similar methodology to the Mexican study and also found no significant differences in AUC or Cmax according to the recommended limits 0.80 – 1.25 (90% CI). (Saavedra 2010 - Abstract only)

Two studies sponsored by Janssen-Cilag (Topamax manufacturers) analysed the medical and pharmacy claims of epilepsy patients treated with topiramate in Canada. The data collected in these studies appears to have some overlap because

they both used data from Re´gie de l'Assurance-Maladie du Que´bec; one from January 2006 to October 2007 and the other between January 2006 and September 2008.

The study reviewing data between January 2006 and September 2008 compared the medical and pharmacy resource utilisation (number of events/person/year) of patients with epilepsy treated with topiramate. 1164 topiramate users were observed on average for 946.1 (SD 110.6) days. Approximately 39% (n=453) switched to generic topiramate, and of which 55.6% received multiple-generic versions and 15.7% switched back to brand. Multiple-generic use was associated with increased utilisation of AEDs (adjusted incidence ratio [IRR] 1.10, p<0.0001) and also non-AED drugs (IRR 1.34, p<0.0001), compared to brand and single-generic use (other AEDs: IRR 1.01, p=0.5487; non-AED prescriptions: IRR 1.28, p<0.0001). The rate of hospitalisation (IRR 1.32, p=0.0003) and length of stay (IRR 1.32, p<0.0001) was also significantly different in the multiple-generic periods of use vs the brand periods.
The authors suggest that multiple-generic substitution of topiramate was associated with significantly higher rates of hospitalisation and pharmacy dispensings and increased direct medical costs. (Paradis Neurology 2009)

The second study between January 2006 and October 2007 investigated the clinical and economic consequences following generic substitution of one vs multiple generics of topiramate. 948 patients on topiramate, of which 70 – 72% were on polytherapy, were observed for an average of 665 days. 37.8% of patients switched to generic topiramate and 12.5% switched back to brand. 23% of the generic users received at least two different generic versions. Compared to brand use, multiple generic use was associated with higher utilisation of other prescription drugs (incidence rate ratio [IRR] 1.27,95% CI 1.24–1.31), higher hospitalisation rates (0.48 vs 0.83 visit/person-year, IRR 1.65,95% CI 1.28–2.13), and longer hospital stays (2.6 vs 3.9 days/person-year, IRR 1.43, 95% CI 1.27– 1.60), but the effect was less pronounced in single-generic use (hospitalisation: IRR 1.08, 95% CI 0.88–1.34, length of stay: IRR 1.12, 95% CI 1.03–1.23). The risk of head injury or fracture was nearly three times higher (hazard ratio 2.84, 95% CI 1.24–6.48) following a generic-to-generic switch compared to brand use. The total annual health care cost per patient was higher in the multiple-generic than brand periods by $1,716 (Canadian) (cost ratio 1.21, p=0.0420). The authors concluded that multiple-generic substitution of topiramate was significantly associated with negative outcomes, such as hospitalisations and injuries, and increased health care costs. (Duh 2009)

Another study based on the same data from Re´gie de l'Assurance-Maladie du Que´bec for 1164 patients between January 2006 and September 2008 predicted that the total healthcare costs would be expected to increase in the UK by 3.5% one year after generic entry. (Paradis Curr Med Res Opin 2009)

A Russian study reviewed 220 epilepsy patients who lost seizure control of 1 year or more duration. Loss of seizure control in 60.4% cases was caused by a switch from brand to generic AED with 28.2% patients being switched to topiramate generics. The investigators also reviewed 160 patients who switched from brand topiramate

to generic and compared to a control group (52 patients) who continued to receive the brand. Following a switch, remission was lost in 75.6% of patients and 51.9% needed emergency care and hospitalisation. Switching back to the original medication was done in 86.2% of patients with increases of initial doses in 58% and transition from mono- to polytherapy in 60%. The baseline level of seizure control was achieved in 32.9% of patients. The fulltext of this study was not available so no further details are available on the generics used or the patients' clinical background and no blood levels were reported. (Rudakova 2011 - Abstract only)

A Polish study reviewed 646 drug-resistant epilepsy patients with partial seizures treated with 1–3 new generation AEDs. Patients were switched from a brand to generic AED. The group included 68 patients on two brand agents switched to generic drugs. There were 182 gabapentin patients, 284 on lamotrigine and 160 on topiramate. The authors concluded that switching any of these drugs to generics did not increase seizure frequency (mean seizure frequency per month before and after a switch was 9.9 vs 9.6 for topiramate (6.7 vs 6.9 for lamotrigine and 8.2 vs 8.0 for gabapentin). The percentage of patients that needed to be switched back to the original medication was between 0 and 2.1%. (Czapinski 2009)

Appendix 8
Review of the evidence for sodium valproate (and salts)

A study used bioequivalence data for approved generic AED formulations in the US provided by the FDA Centre for Drug Evaluation and Research, Office of Generic Drugs. A total of 141 generic AED products were evaluated in 258 bioequivalence studies. Divalproex, Gabapentin and oxcarbazepine had the greatest proportions of bioequivalence studies in which Cmax varied by 15 to 25% between fasting and fed states of different generic products, compared to other AEDs. (Krauss 2011)

A large US retrospective cohort analysis used pharmacy and medical claims and enrolment data from a claims database (Medicare) between 2002 and 2008. Epileptic patients taking divalproex, lamotrigine and phenytoin were studied and divided into cohorts of patients who switched from the brand to a generic version and patients who remained on the same brand AED. Inclusion in the study required > 80% adherence. Each divalproex cohort had 399 patients (after matching 1:1). The majority of divalproex patients in the study had utilised only one AED during the 6-month pre-index period. However, a significant portion (31.1–32.6%) utilised two AEDs and 6.8 – 8.0% utilised three AEDs and les than 2% utilised four AEDs or more.

The incident rate for: discontinuation of AED, dose change of AED, or AED add-on therapy per person-year was 1.02 (95% CI 0.88 -1.42) for divalproex [1.00 (95% CI 0.84–1.19) for lamotrigine and 1.85 (95% CI 1.50 -2.29) for phenytoin].
The event rates of all-cause emergency department visits and hospitalisations per person-year comparing the generic switch cohort with the nonswitch cohort was 0.84 (95% CI 0.66 -1.06) for divalproex, [0.97 (95% CI 0.80 - 1.17) for lamotrigine and 0.96 (95% CI 0.80 -1.16) for phenytoin]

The authors suggest that for similar patient populations taking divalproex, brand to generic switches can be made without risking serious adverse events requiring medical attention. (Erickson 2011)

A Canadian study analysed prescription drug dispensing claims paid for by the Ontario Drug Benefit Formulary to identify patients on lamotrigine, clobazam or valproic acid / divalproex in January 2002 to March 2006. Rates of switch back to brand were determined [Lamictal, Frisium and Depakene (valproic acid; divalproex)] and these were compared with non-AED long-term therapies, antihyperlipidemics and antidepressants.
There were 1770 valproic acid / divalproex patients (719 monotherapy and 1051 polytherapy 59.4%). Depakene (20.9%) and Frisium (20.7%) patients experienced the highest switchback rates, followed by 12.9% for Lamictal patients. The switchback rates for non-narrow-therapeutic-index drugs were substantially lower at 1.5–2.9% for the statins and SSRIs under study. A larger share of polytherapy patients switched back in the case for Depakene (21.3 vs. 20.6%). (Andermann 2007)

A survey of physicians in the US found that 293 (65%) out of 451 neurologists who completed the online survey had a patient who experienced a loss of seizure control caused by either a switch from a brand to a generic AED or from uncontrolled switching between generic forms of an AED. 50/293 cases were chosen randomly for further review. There were 14 patients on valproic acid in the random sample, who were well-controlled on the brand AED, and who subsequently experienced a breakthrough seizure or increased seizure frequency after switching to a generic without other provoking factors. [Two patients were on a combination of two AEDs, both of which were switched to generics (unknown which AEDs)].

The blood levels of those patients who were switched to generic valproic acid decreased by an average of 34% (compared to carbamazepine 20% and phenytoin 40%). 3 patients had blood levels after switching back to brand and levels returned to within 10% of the original baseline level. (Berg 2008)

There are case reports in India of two mentally retarded adults suffering (myoclonic and generalised tonic clonic) seizures since childhood who were treated with generic sodium valproate 200 mg bd and gradually increased to 1600mg/day and 1400mg/day in three divided doses over a period of 1½ years. For 2 consecutive months, they were maintained on the same dose. The seizures occurred at a frequency of 4/month and 2/month respectively. The serum level of the free valproic acid was 67.87 mcg/ml and 71.16 mcg/ml respectively. A branded form of sodium valproate was substituted for the generic form in the same dose and interval for a period of one month. At the end of one month, the seizure frequency was 2 and 1 per month and the repeat serum level of free valproic acid was 118.40 mcg/ml and 80.58 mcg/ml respectively. No adverse effects were noticed. (Dhanaraj 2004)

Appendix 9: Identifying the manufacturer of phenytoin tablets and capsules outside of the packaging

These tables contain images of phenytoin formulations to help identify medicines in dosette boxes.

Table 1: Phenytoin Capsule Identification

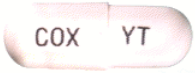
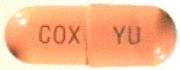
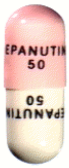
Capsules	Image	Description
Phenytoin 100mg capsules; NRIM		100mg Capsule. Hard gelatin capsules with an orange transparent coloured cap printed with “146” and white coloured body, containing white granular powder. The length is 15.8mm.
Phenytoin 50mg capsules; Actavis		50mg Capsule. The size is 14.3 mm x 5.2mm x 4.9mm (from Oct 92)
Phenytoin 100mg capsules; Actavis		100mg Capsule. The size is 15.5 mm x 5.5 mm x 5.3mm (from Jan 92)
Epanutin capsules 25mg (phenytoin); Pfizer Limited / Flynn Pharma Ltd		25mg Capsules: A white powder in a No 4 hard gelatin capsule with a white opaque body and blue-violet (purple) cap, radially printed 'EPANUTIN 25'. The size is 13.6mm x 5.2mm x 5.0mm
Epanutin capsules 50mg (phenytoin); Pfizer Limited / Flynn Pharma Ltd		50mg Capsules: A white powder in a No 4 hard gelatin capsule with a white opaque body and a flesh-coloured transparent (pink) cap, radially printed 'EPANUTIN 50'. The size is 13.7mm x 5.1mm x 4.9mm
Epanutin capsules 100mg (phenytoin); Pfizer Limited / Flynn Pharma Ltd		100mg Capsules: A white powder in a No 3 hard gelatin capsule with a white opaque body and orange cap, radially printed 'EPANUTIN 100'. The size is 15.4mm x 5.6mm x 5.5mm
Epanutin capsules 300mg (phenytoin); Pfizer Limited / Flynn Pharma Ltd		300mg Capsules: A white powder in a No 1 hard gelatin capsule with a white opaque body and green cap, radially printed 'EPANUTIN 300'. The size is 18.8mm x 6.8mm x 6.4mm
Phenytoin 100mg tablets; Milpharm Ltd	No Image available	Film-coated tablet. White to off-white, oval shaped, film-coated tablets debossed with 'C' on one side and '70' on the other side. The size is 11.6 mm x 6.5 mm.

Table 2: Phenytoin Tablet Identification

Tablets	Image	Description
Phenytoin 100mg tablets; Wockhardt		White, round shaped. The size is 8.7 mm x 5.0mm (from Dec 09)
Phenytoin 100mg tablets; Teva UK		White, round shaped, tablets printed with '100 2302'. The size is 8.5mm x 4.9mm (from Nov 07)
Phenytoin 100mg tablet; Actavis		100mg tablet. White, round shaped. The size is 8.3 mm x 5.7 mm (from Feb 91)
Epanutin Infatabs (phenytoin); Pfizer Limited	 Older version does not have P-D 007 marking: 	A yellow triangular chewable tablet with flat sides, a bevelled edge and a breaking line on one side with P-D 007 imprinted on the other side. The tablet triangular perimeter 10.7mm x 10.7mm x 10.7mm

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