Formulation switching of antiepileptic drugs
A Report on the Recommendations of the Commission on Human Medicines from July 2013

Executive summary
This report concerns CHM’s recommendations on issues relating to brand/generic prescribing and switching between formulations for antiepileptic drugs (AEDs). There are particular concerns for AEDs because a number of them have a narrow therapeutic index and the consequences of therapeutic failure can be very severe.

The practical and regulatory implications for the MHRA, the Pharmaceutical Industry and DH are identified and discussed.

The paper includes proposals for:
- A categorisation of antiepileptic drugs by risk relating to formulation switching
- Requirements for naming and presentation (labelling) of AEDs
- Handling parallel imported products and own label supplier products
- Suggested wording for the BNF
- Information for publication on the MHRA website
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1. Background

Normally, if a generic medicinal product is shown to be bioequivalent to the innovator product, as defined by the relevant regulations and guidelines, it follows that the product should be considered to be clinically equivalent. Concerns have been raised that demonstration of bioequivalence, even according to the more stringent regulatory standards for drugs considered to have a narrow therapeutic index, might be insufficient to exclude the possibility of clinically important non-equivalence to the innovator product for certain antiepileptic drugs (AEDs). Therefore prescribing by specific named product might be necessary.

An ad hoc Expert Group of the Commission on Human Medicines was set up to consider a range of issues relating to brand/generic prescribing including, specifically, requirements for antiepileptic drugs.

A review of a number of published studies on the issue of potential harm arising from generic substitution of AEDs did not show clear evidence of actual harm arising from switching formulations. However the lack of robust evidence of harm does not exclude the possibility that significant harm may sometimes occur, given the inherent limitations in the design of these mostly observational studies, as already reflected in the BNF with regard to phenytoin and carbamazepine, and more generally in the NICE AED guidance.

The Group considered the bioequivalence rules that are applied to generic AEDs and the possible implications for clinical efficacy and safety of the differences in bioavailability of different formulations that were compatible with the regulations (including switching from branded originator to generic products and also between different generic products). The Group also considered the significance of the solubility and permeability of the drug substance (BCS classification) in terms of its susceptibility to formulation dependent differences in bioavailability.

The Group expressed a view that in general terms there was a need to maintain continuity of supply of a specific product for certain AEDs. The specific product could be either a branded product or a generic. Continuity of supply from the same manufacturer was the key issue, rather than whether the product was branded or a generic.

AED Categorisation

It was recognised that all AEDs are not the same in this respect. Problems related to small differences in bioavailability of different manufacturers products (branded, generic) are of concern for some drugs (most notably phenytoin) 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 e.g. phenytoin, carbamazepine
- Category 2 - possible concerns e.g. lamotrigine, topiramate, valproate
- Category 3 - unlikely to be concerns e.g. levetiracetam, lacosamide, pregabalin gabapentin

The Group noted that the measures necessary to ensure the necessary continuity of supply should also consider the advice in the recently revised NICE guideline:

"Consistent supply to the child, young person or adult with epilepsy 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’ (BNF; available at http://bnf.org) on the bioavailability and pharmacokinetic profiles of individual AEDs, but note that these do not give information on comparing bioavailability of different generic preparations".
Category 1 - 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. a generic approved with a brand name) or a specified manufacturer’s generic product.

Category 2 – according to clinician's judgement, as per NICE guideline.

Category 3 - 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).

The Group proposed that the BNF should be asked to include this guidance in the relevant section. The advice will need careful wording of text to ensure the message that continuity of supply from the same manufacturer is clearly stated to be the key issue rather than whether the product is branded or generic. There was agreement that terms such as “branded generic” should be avoided since this could lead to confusion.

The Group queried whether computerised GP prescribing systems would allow the practitioner to select a specific manufacturer for a generic AED to ensure that consistency of supply was maintained. Subsequent discussion with Department of Health (DH) colleagues confirmed that current systems are capable of allowing this degree of specificity but that further investigation of the practicalities of introducing the proposed measures would be required. It was noted that prescribing to maintain continuity of supply will already be occurring to some extent based on NICE guidance.

At its meeting in March 2012 the Commission on Human Medicines (CHM) endorsed the recommendations of the Ad Hoc group in relation to AEDs. The CHM noted concerns regarding generic substitution of some medicinal products in this class, relating primarily to the very severe consequences of therapeutic failure and the narrow therapeutic index of certain AEDs. Another consideration is that, other than plasma drug level monitoring, there is no available clinical indicator to predict risk of seizures.

An informal consultation with trade associations and industry was undertaken by the MHRA during 2012. It covered both general aspects concerning the practicalities of implementing measures to ensure continuity of supply of a specific product to patients and aspects specific to AEDs. Based on the feedback received the measures proposed do appear to be workable in practice.

A review of all currently approved AEDs was conducted by the MHRA with a view to categorising each into one of the three risk groups described above. By default drugs fell into category 2 unless the available information established either that there were particular issues necessitating the more robust measures for category 1, or that the risk of clinically significant differences between formulations was very low (category 3).
2. Practical and regulatory implications

If the overarching proposal of maintaining the continuity of supply of AEDs based on categorisation principles and clinical judgement is adopted this would require some changes to the current regulatory procedures within the MHRA (including associated practical measures required of affected Marketing Authorisation Holders [MAH]) and DH prescribing systems. The main practical and regulatory considerations are as follows:

MHRA

a) Product naming convention:

Current naming convention in the UK allows for the product name to be (i) a brand name, or (ii) the international non-proprietary name (INN) or (iii) the INN + the name of the MAH (or distributor).

Provided prescribing systems are enabled so that the different manufacturers of a particular generic can be selected at the point of prescribing then it might be possible that the current naming conventions could stand. Alternatively, the MHRA may consider it necessary to require that all generic products of AEDs are named as INN + MAH such that the need for continuity of supply of a particular manufacturer (as denoted by the brand name or presence of the MAH name) is made clear when prescribing at the product name level. This naming convention is consistent with Directive 2001/83/EC and EU practice and thus would have no wider implications.

b) Own Label Suppliers (OLS):

Current UK practice allows for multiple distributors to be present on a single product licence each of which may have their own livery and associated product name. Given the proposed need for continuity of supply, the potential for the same distributor to be named on multiple licences for the same AED (for products which may be of different formulations) means that it would not be possible to distinguish between those different licences using only the name of the distributor and the INN. Furthermore, the use of INN + Distributor would increase the overall number of apparently different treatment options which may present supply (availability) difficulties. For this reason it is proposed that the use of OLS for AEDs would no longer be allowed and any OLS on currently granted licences would be removed.

c) Product Licensing - Parallel Imports (PLPI)

The UK PLPI processes would need to be reviewed to provide ongoing assurance that all PLPI AEDs are interchangeable with the UK reference product taking into account the 3 categories proposed and that they are labelled accordingly. For example reassurance that Epilim and Epilim PLPI are interchangeable.

The naming of PLPI products using the INN+MAH convention presents 2 further issues:

1. Using INN + PLPI MAH as the product name would not allow the prescriber to identify the original MAH of that product. Three parallel importers importing the same identical product would result in that single product having 3 different ‘PLPI’ names on the UK market in addition to the equivalent UK product

2. Conversely the PLPI company could hold licences for two different generic products of a single AED which would then have the same name:

Including the PLPI MAH in the product name would therefore not be helpful in ensuring continuity of supply of a specific formulation. It is proposed instead that PLPIs are named according to their UK equivalent product e.g.

- the UK brand name (primarily in the case of PLPI’s of the branded originator product) or
- INN + UK MAH (primarily in the case of PLPI’s of generic products).
DoH

i) Prescribing systems:

As indicated above, Healthcare professionals must be able to prescribe according to the need to maintain a consistent supply. Prescriptions will need to reflect this such that the appropriate product is dispensed. Vendors of prescribing software will need to be made aware of this change to prescribing practice if they have not already given the NICE guidance recommendations.

ii) Communications:

In addition to BNF, DSU articles and MHRA publications a further Communications strategy will be required to ensure that healthcare providers are aware of the change in prescribing practice (with reference to the afore mentioned publications and the NICE guidance). It is noted that prescribing to maintain continuity of supply will already be occurring to some extent based on NICE guidance. Patient information and education measures will also need to be implemented.

3. A proposed categorisation of antiepileptic drugs by risk relating to formulation switching

The information presented below is based on a review of the product information for the brand leader products and of information from standard texts and review articles relating to the therapeutic index of each drug and relevant physicochemical characteristics.

There is no universally accepted definition of a narrow therapeutic index drug (NTID) and the bioequivalence guideline does not define a specific set of criteria for regulatory purposes (a case by case approach is adopted based on clinical considerations). A definition that has some value is a drug for which the ratio between the dose associated with toxicity and the normal therapeutic dose <2. However clearly this can vary substantially from patient to patient. Titration to the maximum tolerated dose in patients still reporting seizures at average daily dose is common with AED treatment. This can provide useful information on the therapeutic index of the drug.

The key physicochemical characteristics of a drug that are indicative of a potential risk of formulation differences in extent and/or rate of absorption are the solubility of the drug substance and its permeability across membranes. These aspects form the basis of the Biopharmaceutical Classification System in which drugs are divided into four classes; high solubility/high permeability (Class 1, optimal class with lowest risk of absorption variability), low solubility/high permeability (Class 2), high solubility/low permeability (Class 3) and low solubility/low permeability (Class 4). BCS Class 1 drugs are very unlikely to show meaningful differences between formulations and can be placed in category 3 unless they have a narrow therapeutic index.

The clinical value of therapeutic drug monitoring in each case is noted although this does not necessarily correlate with a narrow therapeutic index or a risk of clinically significant formulation differences.

The potential for drug-drug interactions is an important consideration especially when a patient is taking one or more of the older drugs. Carbamazepine, phenytoin, phenobarbital and primidone induce a variety of cytochrome P450 (CYP) enzymes (including CYP1A2, CYP2C9, CYP2C19 and CYP3A4) as well as glucuronyl transferases (GT) and epoxide hydrolase. Valproic acid is a CYP inhibitor. These AEDs are metabolized by these same enzyme systems so bi-directional drug-drug interactions occur when they are administered concomitantly. Compared with older generation agents, the recently developed AEDs cause less induction or inhibition of these enzymes. Most but not all of the newer AEDs are metabolized by CYP enzymes so are susceptible to drug-drug interactions with enzyme inducing AEDs.
Category 1

Phenytoin

Phenytoin is considered to be a low solubility drug for the purpose of BCS classification. It is reported to be incompletely absorbed from the small intestine after oral administration. Various formulation factors may affect the bioavailability of phenytoin and the parameters controlling elimination are also subject to wide inter-individual variation. Based on the available data phenytoin is classified as BCS class 4.

Phenytoin should be introduced in small dosages with gradual increments until control is achieved or until toxic effects appear. Dosage needs to be individualised as there may be wide inter-individual variability in phenytoin serum levels with equivalent dosage. Dose limiting undesirable effects are often seen at doses required for optimal efficacy.

Phenytoin’s hepatic metabolism is reliant on a saturable enzyme system which results in zero order kinetics within the therapeutic range. At the upper end of therapeutic levels a small change in dose delivered to the circulation can result in disproportionately large changes in plasma concentrations.

Phenytoin induces many cytochrome P450 (CYP) and glucuronyl transferase (GT) enzymes and is associated with substantial drug-drug interactions, in particular with other AEDs including carbamazepine, valproate, lamotrigine and tiagabine.

The BNF currently states the following for phenytoin: “Note: On the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients”.

Carbamazepine

Carbamazepine is considered to be a low solubility drug for the purpose of BCS classification. It is absorbed almost completely but relatively slowly from the GI tract and bioavailability from various oral formulations has been reported to lie between 85-100%. On this basis the likely classification of carbamazepine is BCS class 2. It has been noted in brand leader SPCs (Tegretol) that different preparations may vary in bioavailability and so, to avoid reduced effect or risk of breakthrough seizures or excessive side effects, it may be prudent to avoid changing the formulation.

The steady-state plasma concentrations of carbamazepine considered as “therapeutic range” vary considerably inter-individually; for the majority of patients a range between 4-12µg/ml corresponding to 17-50µmol/l has been reported. Carbamazepine plasma levels greater than 8.5µg/mL have been associated with toxicity and dose limiting undesirable effects are often seen at doses required for optimal efficacy. Carbamazepine is considered to have a narrow therapeutic index.

Carbamazepine induces many cytochrome P450 (CYP) and glucurononyl transferase (GT) enzymes and is associated with substantial drug-drug interactions, in particular with other AEDs including phenytoin and valproate.

The BNF currently states the following for carbamazepine: “Different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation”.

Phenobarbital

Phenobarbital is readily absorbed from the gastrointestinal tract with a reported oral bioavailability of about 90%. There is a lack of reliable data on the solubility of phenobarbital. It is relatively lipid insoluble but there is a lack of reliable data on its aqueous solubility. One publication in the literature has classified it as BCS class 1 but it is
probably safer to consider it as BCS class 2 based on the limited information.

Phenobarbital has a very long elimination half-life (5 days) and therefore differences between rate of absorption (reflected in single dose Cmax) will have little effect in practice.

There is considerable inter-individual variation in phenobarbital kinetics and tolerance will develop with chronic use. According to the BNF the target range for plasma-phenobarbital concentration for optimum response is 15–40 mg/litre (60–180 micromol/litre) although plasma-drug level monitoring is complicated by the development of tolerance.

Toxicity varies between patients but dose limiting undesirable effects are often seen at doses required for optimal efficacy. Features of poisoning are to be expected after ingestion of 1g in adults, which is five times the recommended daily dose.

Phenobarbital induces many cytochrome P450 (CYP) and glucuronyl transferase (GT) enzymes and is associated with substantial CYP 3A4 mediated drug-drug interactions, in particular with other AEDs including phenytoin, carbamazepine and valproate.

Phenobarbital might be considered to be close to the threshold of categories 1 and 2. Although its high permeability, apparently fairly good solubility, and very long half-life are all favourable factors regarding the potential for formulation differences to result in major PK differences, the very narrow therapeutic index of the drug is of concern. For this reason it has been placed in category 1.

Primidone

Primidone is poorly soluble in water (60 mg per 100 ml at 37° C) and in most organic solvents. It is stated to be well absorbed from the gastrointestinal tract (close to 100% bioavailable) and is well distributed in all organs and tissues. Primidone clearly seems to fall into BCS class 2.

The pharmacokinetics of primidone are complex because of biotransformation into two metabolites, phenobarbital (major) and phenylethylmalonamide (minor), that have anticonvulsant activity and complex pharmacokinetic properties. The percentage of primidone converted to phenobarbital has been estimated to be 15% in humans. Induction of primidone metabolism by other enzyme-inducing AEDs (e.g. phenytoin) results in increased serum concentrations of the active metabolite phenobarbital. Primidone has anticonvulsant activity of its own. The extent to which the active metabolite phenobarbital contributes to the overall anticonvulsant efficacy of primidone is rather unclear and no data could be found on plasma levels of the parent and metabolites at steady state. It is noted that the apparent half-life of primidone (approximately 8 hours) is much shorter than that of phenobarbital.

As phenobarbital is a potent enzyme inducer, primidone is associated with similar drug-drug interactions.

Primidone has a wider therapeutic dose range and therapeutic index than that of Phenobarbital and is much less toxic in overdose than phenobarbital. However its poor solubility is a concern in the context of formulation switching. Primidone might also be considered to be close to the threshold of categories 1 and 2 but is placed in category 1 for the reasons outlined above.

Category 2

Sodium Valproate

Reliable data on solubility are unavailable. However some publications have classified valproate as BCS class 2 (low solubility, high permeability). Literature references indicate that it has an absolute bioavailability of about 100%. It is therefore BCS class 2 or 4.

Optimal dosage is mainly determined by seizure control. Measurement of plasma levels is considered unnecessary.
as a routine but may occasionally be required, especially in cases of polypharmacy with enzyme inducing AEDs. The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). Plasma levels above the effective therapeutic range are associated with an increased incidence of adverse effects. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. The pharmacological (or therapeutic) effects of sodium valproate may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Valproic acid may cause clinically relevant drug-drug interactions by inhibiting drug metabolizing enzymes, most notably with phenobarbital (CYP2C9 and CYP2C19) and lamotrigine (Glucuronyl transferase type 1A4). It can approximately double serum lamotrigine levels and increase serum phenobarbital levels by about 30–50%.

Sodium valproate might be considered to be close to the threshold of categories 1 and 2. The previous recommendation of the ad hoc expert Group and of the CHM was to place it in category 2 and this review did not find reason to revise that recommendation.

**Lamotrigine**

Lamotrigine is considered to be a low solubility drug for the purpose of BCS classification. It is rapidly and completely absorbed from the gut (close to 100% bioavailability) with no significant first-pass metabolism. The extent of absorption is unaffected by food. The pharmacokinetics of lamotrigine are linear up to 450 mg, the highest single dose tested. Based on this information lamotrigine can be classified as BCS class 2.

There is considerable inter-individual variation in steady state maximum concentrations but within an individual, concentrations rarely vary substantially. Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose has been reported with no permanent sequelae. The therapeutic index of lamotrigine appears to be somewhat wider than for the AEDs classified here in category 1 but not as wide as some of the newer agents classified in category 3. It is not considered to be a narrow therapeutic index drug.

**Perampanel**

Perampanel is considered to be a low solubility drug for the purpose of BCS classification. It is rapidly and essentially completely (close to 100%) absorbed after oral administration with no evidence of marked first-pass metabolism. Food does not affect the extent of absorption. Plasma concentrations of perampanel increase in direct proportion to administered doses over the range of 2 to 12 mg. Perampanel can be classified as BCS class 2.

Perampanel has a wide therapeutic dose range. It is not considered to be a narrow therapeutic index drug.

**Retigabine**

Retigabine is considered to be a low solubility drug for the purpose of BCS classification. It is rapidly absorbed. Absolute oral bioavailability of retigabine relative to an intravenous dose is approximately 60%. Retigabine pharmacokinetics are essentially linear over the single dose range of 25 to 600 mg in healthy volunteers and up to 1,200 mg daily in patients. Retigabine can be classified as BCS class 4.

Retigabine has a wide therapeutic dose range. Overdoses in excess of 2,500 mg/day were reported during clinical studies, with no residual sequelae. It is not considered to be a narrow therapeutic index drug.

**Rufinamide**

Rufinamide is considered to be a low solubility drug for the purpose of BCS classification. It is well absorbed when taken with food, with an absolute bioavailability between 70% and 85%. This does not
meet the BCS criteria for high permeability. The AUC of rufinamide increases less than proportionally with doses in both fasted and fed healthy subjects and in patients, probably due to dose-limited absorption behaviour. As dose increases the bioavailability decreases. Rufinamide is almost exclusively eliminated through hydrolytic metabolism. Rufinamide can be classified as BCS class 4.

It has a wide therapeutic range and in overdose, multiple dosing of 7,200 mg/day was associated with no major signs or symptoms.

**Clobazam**

Clobazam is a benzodiazepine. Reliable data on solubility are unavailable. Clobazam is fairly well absorbed after oral administration. Literature references quoted estimates of absolute oral bioavailability between 60% and 87%. Alcohol is reported to decrease oral bioavailability by 50%. Clobazam is considered to be a low permeability drug for the purpose of BCS classification.

As with other benzodiazepines, plasma levels do not correlate well with either therapeutic response or side-effects. It is not considered to be a narrow therapeutic index drug.

**Clonazepam**

Clonazepam is a benzodiazepine. It is considered to be a low solubility drug for the purpose of BCS classification. It is quickly and completely absorbed after oral administration; measured oral bioavailability is 90%. Based on this information clonazepam can be classified as BCS class 2.

Routine monitoring of plasma concentrations of clonazepam is of unproven value since this does not appear to correlate well with either therapeutic response or side-effects. Clonazepam is not considered to be a narrow therapeutic index drug.

**Oxcarbazepine**

Oxcarbazepine is considered to be a low solubility drug for the purpose of BCS classification. Following oral administration it is completely absorbed (close to 100% bioavailability). Based on this information oxcarbazepine can be classified as BCS class 2.

Oxcarbazepine has a relatively wide therapeutic dose range. Therapeutic effects are seen at doses between 600 mg/day and 2400 mg/day. Isolated cases of overdose have been reported. The maximum dose taken was approximately 24000 mg. All patients recovered with symptomatic treatment.

Oxcarbazepine stimulates the glucuronyl transferase mediated metabolism of lamotrigine. It is also a weak inhibitor of CYP2C19, and may increase by this mechanism the plasma levels of phenytoin (by up to 40%) and, to a lesser extent, phenobarbital.

**Eslicarbazepine Acetate**

Eslicarbazepine is considered to be a low solubility drug for the purpose of BCS classification.
Eslicarbazepine acetate is a prodrug which is rapidly and extensively biotransformed to its major active metabolite S-licarbazepine by hydrolytic first-pass metabolism. Following oral administration, plasma levels of eslicarbazepine acetate usually remain below the limit of quantification. Bioavailability is considered high since the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine dose. This meets the BCS criteria for high permeability. Eslicarbazepine acetate can be classified as BCS class 2.

Peak plasma concentrations (C_{max}) of S-licarbazepine are attained at 2-3 hours post-dose and steady state plasma concentrations are attained after 4 to 5 days of once daily dosing, consistent with an effective half-life in the order of 20-24 h.

Eslicarbazepine is not considered to be a narrow therapeutic index drug.

Zonisamide

Zonisamide is considered to be a low solubility drug for the purpose of BCS classification. It is almost completely absorbed after oral administration. The first-pass metabolism is believed to be negligible. Absolute bioavailability is estimated to be approximately 100% and is not affected by food. Kinetics are linear over the therapeutic dose range. Zonisamide is classified as BCS class 2.

No clear zonisamide dose-concentration-response relationship has been defined. It is not considered to be a narrow therapeutic index drug.
Topiramate

Topiramate is considered to be a low solubility drug for the purpose of BCS classification. It is reported in the Topamax SPC to be rapidly and well absorbed. Pharmacokinetics are linear over a 100 to 400 mg single oral dose range in healthy subjects. According to the NCIB website the absolute oral bioavailability of topiramate in humans is 81-95%. Topiramate can therefore be conservatively classified as BCS class 3 as the data on permeability (bioavailability) are insufficient to confirm BCS class 1 (cited thresholds are 85% or 90%).

It is not necessary to monitor topiramate plasma concentrations to optimize therapy with Topiramate. It does not have a particularly narrow therapeutic index.

Topiramate is considered to be close to the threshold of categories 2 and 3. The previous recommendation of the ad hoc expert Group and of the CHM was to place it in category 2.

Category 3

Levetiracetam

Levetiracetam is considered to be a high solubility drug for the purpose of BCS classification. It is also a highly permeable compound and its classification as BCS class 1 has been confirmed by the CHMP. The pharmacokinetic profile is linear with low intra- and inter-subject variability (as has consistently been seen in bioequivalence studies).

Levetiracetam has not been reported to cause or be a target for clinically relevant pharmacokinetic drug interactions.

The therapeutic index of levetiracetam is relatively wide.

Lacosamide

Lacosamide is considered to be a high solubility drug for the purpose of BCS classification. It is rapidly and completely absorbed after oral administration, with oral bioavailability of approximately 100%. The available data seem to be sufficient to confirm classification as BCS class 1.

Lacosamide is predominately renally eliminated as unchanged drug. It has minimal CYP 450 interactions. Lacosamide is not considered to be a narrow therapeutic index drug.

Tiagabine

Tiagabine is considered to be a high solubility drug for the purpose of BCS classification. It is rapidly and virtually completely absorbed from the GI tract, with an absolute bioavailability of 89% (linear within the therapeutic dose range). This meets the criteria for classification as a highly permeable drug. It is therefore classified as BCS class 1. Tiagabine is not considered to be a narrow therapeutic index drug.
Gabapentin

Gabapentin is considered to be a high solubility drug for the purpose of BCS classification. Its bioavailability tends to decrease with increasing dose which imparts non-linearity to pharmacokinetic parameters. At therapeutic doses it seems to be sufficiently well absorbed to qualify as BCS class 1.

Acute, life-threatening toxicity has not been observed in overdoses with gabapentin of up to 49 grams. Gabapentin is considered to have a relatively wide therapeutic index.

Gabapentin is eliminated unchanged solely by renal excretion and has not been reported to cause or be a target for clinically relevant pharmacokinetic drug interactions. The therapeutic index of gabapentin is relatively wide.

Pregabalin

Pregabalin is considered to be a high solubility drug for the purpose of BCS classification. It is well absorbed orally, and exhibits dose proportional linear pharmacokinetics. Based on the available data pregabalin can be considered to be BCS class 1.

Pregabalin is excreted almost entirely unchanged in the urine and exhibits low inter-individual pharmacokinetic variability. It has a relatively wide dose range and when taken in overdose no adverse events have been recorded at doses 25x the maximum recommended dosage. Pregabalin does not have a narrow therapeutic index. It is renally cleared and has not been reported to cause or be a target for clinically relevant pharmacokinetic drug interactions.

Pregabalin is not considered to be a narrow therapeutic index drug.

Ethosuximide

Ethosuximide is considered to be a high solubility drug for the purpose of BCS classification. It is readily absorbed from the gastro-intestinal tract. Based on the available data ethosuximide can be considered to be BCS class 1. It extensively metabolised in the liver and is excreted in the urine mainly in the form of its metabolites. Therapeutic doses are usually between 1000-1500mg daily.

The therapeutic index of ethosuximide is somewhat wider than for the other “old” AEDs. It is not considered to be a narrow therapeutic index drug.

Vigabatrin

Vigabatrin is a water soluble compound and is considered to be a high solubility drug for the purpose of BCS classification. It is rapidly and completely absorbed from the gastrointestinal tract and food administration does not alter the extent of absorption. The available data seem to be sufficient to confirm classification as BCS class 1.

No direct correlation exists between the plasma concentration and the efficacy.

Vigabatrin is renally cleared and has not been reported to cause or be a target for clinically relevant pharmacokinetic drug interactions.

Vigabatrin is not considered to be a narrow therapeutic index drug.
4. Suggested wording for the BNF*

It is proposed to include boxed MHRA / CHM Advice in the introductory section “control of epilepsy”. In addition for AEDs classified in this paper as category 1 (specific measures advised) it is proposed to include an additional warning (to be discussed whether this would also be boxed) under the individual drug headings. In the case of phenytoin and carbamazepine this would replace the existing drug specific warnings.

The following are initial proposals and have not yet been discussed with the BNF.

*The suggested wording below reflects the proposal at the time of the CHM meeting in July 2013 and has now been superseded

General advice

<table>
<thead>
<tr>
<th>MHRA / CHM Advice (date) Switching between formulations of antiepileptic drugs (AEDs)</th>
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<tbody>
<tr>
<td>For some AEDs there is a need to maintain continuity of supply of a specific product to ensure a consistent therapeutic effect, whilst for some others switching between formulations is unlikely to have significant clinical consequences. AEDs have been classified into 3 categories of risk, based primarily on their therapeutic index, pharmaceutical aspects (in particular solubility) and the rate and extent of drug absorption (relates to drug permeability):</td>
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<tr>
<td><strong>Category 1</strong>: phenytoin, carbamazepine, phenobarbital, primidone. Specific measures are necessary to ensure consistent supply of a particular product (which could be either a branded product or a specified manufacturer’s generic product).</td>
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<tr>
<td><strong>Category 2</strong>: by default AEDs not listed for categories 1 or 3. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with patient and/or carer.</td>
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<tr>
<td><strong>Category 3</strong>: levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin. No specific measures are normally required and these AEDs can be prescribed generically and without specifying a specific manufacturer’s product.</td>
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Advice under specific product headings

<table>
<thead>
<tr>
<th>MHRA / CHM Advice</th>
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<tr>
<td>(Drug name) is a narrow therapeutic index drug and different preparations may vary in bioavailability. Specific measures are necessary to ensure consistent supply of a particular product (which could be either a branded product or a specified manufacturer’s generic product).</td>
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</table>
5. Information for publication on MHRA website

The CHM recommended that further information supporting the advice on AEDs be made available via the MHRA website. A link to the website is attached below: