348. | April 2024 | 2.0

PrescQIPP
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Antiepileptic drugs: Appropriate switching and safety considerations

Approximately £376 million is spent annually on antiepileptic drugs (AEDs) in England, Wales, Scotland, Northern Ireland and Isle of Man (NHSBSA Oct-Dec 2023 and Public Health Scotland Aug-Oct 2023). Appropriately switching antiepileptic drugs (AEDs) to less costly generic or brand equivalents, or to safer alternatives can free up resources to be used for other NHS services for patients. In addition, appropriate switching may be needed when there are AED stock shortages. Ensuring any switches are undertaken using shared decision making with patients and within current guidance on switching AEDs will negate any potential harms to, or concerns from, patients.

Recommendations

- Secondary care specialists should provide advice in the 'action for GP' section of the discharge summary or outpatient letter to the GP whether a generic AED preparation is suitable for the patient or whether a particular generic manufacturer or brand is necessary.
- When considering switching AEDs used to treat epilepsy consider the following:
  - Advice from the specialist on whether a particular brand or generic manufacturers product should be prescribed.
  - Medicines and Healthcare products Regulatory Agency (MHRA) advice on switching between different manufacturers' products for the three categories of AEDs.
  - United Kingdom Clinical Pharmacy Association (UKCPA) and the Pharmaceutical Market Support Group (PMSG) principles for switching and consensus advice on points to consider when switching.
- Prescribe a branded AED for use in epilepsy where no generic alternative is available.
- Patients receiving AEDs in categories 2 and 3 for epilepsy should be considered for switching where there are no contraindications or concerns following clinical judgement and including patient/carer factors, seizure frequency and treatment history.
- Consider a switch to generic AEDs for all AEDs prescribed for non-epilepsy indications, e.g. pregabalin/gabapentin for neuropathic pain as the MHRA guidance is not applicable to non-epilepsy indications. This should be discussed with the patient in advance.
- Any switch to a generic AED should be fully discussed with the patient to gain their agreement with the switch, reduce the risks of nonadherence and anxiety caused by the switch. Blanket AED switches without individual patient consideration are not recommended.
- Provide suitable patient information, for example the MHRA patient letter Antiepileptic drugs: changing between different manufacturers' products, to help patients with any concerns.
- Community pharmacies should be fully informed in order to gain their support for the switch process and to help alleviate potential patient concerns.
- Consider initiating a generic AED following recent loss of seizure control where extra (adjunctive therapy) or a new AED will be prescribed (even those where a switch is not recommended).

Recommendations

- Before considering any brand to generic switches for valproate, first ensure that the new national patient safety advice has been followed for male and female patients under the age of 55 years.
- Integrated Care Boards (ICBs), Health Boards ((HBs) in Scotland and Wales), and Health and Social Care Trusts (in Northern Ireland) should ensure that responses to the valproate National Patient Safety Alert have been completed.
- Prescribers should familiarise themselves with, and follow the new regulations, and provide patients with information about the risk of taking valproate medicines during pregnancy. As a precaution, male patients on valproate who are planning a family in the next year should talk to their healthcare professional about their treatment.

Background

Disease burden

Epilepsy is one of the most common serious neurological disorders[1] affecting approximately 600,000 people in the UK.[2] The prevalence of active epilepsy in the UK is estimated to be five to 10 people per 1,000 population. The incidence is highest in infants and people aged over 50 years.[1] Complications of epilepsy include injuries, depression and anxiety disorders, absence from school or work and sudden unexpected death in epilepsy (SUDEP), where a person with epilepsy dies suddenly without an identifiable cause.[3]

Epilepsy imposes a large economic burden on patients and their families. Discrimination against patients and their families, social isolation, emotional distress, dependence on family, poor employment prospects and personal injury add to the suffering.[4]

Approximately 70% of children and adults will be seizure free for five years on or off drug treatment, but 30% will have ongoing seizures. In some people who remain seizure free for more than two years, medication can be slowly withdrawn, although AED withdrawal is associated with an increased risk of seizure recurrence.[5] Refer to the section on antiepileptic withdrawal for more information.

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. This confounds the determination of the impact of brand to generic switching and makes recommendations problematic.[6]

Selecting AEDs

Ideally, AEDs should fully control seizures, be well tolerated with no long term safety problems (such as teratogenicity, hypersensitivity reactions, or organ toxicity), and be easy for clinicians to prescribe and patients to take (once or twice daily, no drug interactions, and no need for serum monitoring). The introduction of more than 15 AEDs since the 1980s has provided more choice but has made it more difficult, even for epilepsy specialists, to select the optimum drug for individual patients because each drug has its advantages and limitations.[4]

Valproate (Epilim®, Depakote® and other generic brands) exposure during pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability. Since 2018, valproate has been contraindicated in women of childbearing potential unless the Pregnancy Prevention Programme (PPP) is in place, and only used if there are no other effective treatments available. From January 2024 regulatory changes for oral valproate medicines means that:

- Valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply.
- At their next annual specialist review, women of childbearing potential and girls should be reviewed using a revised valproate Risk Acknowledgement Form, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with one specialist unless the patient's situation changes.[7] Refer to the section on sodium valproate for further information.

Table 1 summarises the use of AEDs in pregnancy and the outcomes where known to aid selection of AEDs in people wanting to become pregnant at some point in time.

Table 1. Summary AED use in pregnancy[8]

AED	Pregnancy outcome
Carbamazepine	Use during pregnancy increases the risk of physical birth abnormalities compared with the general population.
Clobazam	May slightly increase the risk of a baby being born with physical birth abnormalities, however, the research that is available does not allow firm conclusions to be reached and the risk of harming a baby cannot be confirmed or ruled out.
Gabapentin	May slightly increase the risk of a baby being born with physical birth abnormalities.
Lamotrigine	Does not increase the risk of physical abnormalities compared with the general population. Safer to use during pregnancy than other AEDs.
Levetiracetam	Does not increase the risk of physical abnormalities compared with the general population. Safer to use during pregnancy than other AEDs.
Phenobarbital	Use during pregnancy increases the risk of physical birth abnormalities compared with the general population Increase the risk of the baby being born smaller than expected compared with the general population. Increases the risk the child may have difficulties with learning and thinking ability.
Phenytoin	Use during pregnancy increases the risk of physical birth abnormalities compared with the general population. Increases the risk the child may have difficulties with learning and thinking ability.
Pregabalin	May slightly increase the risk of a baby being born with physical birth abnormalities.
Topiramate	Use during pregnancy increases the risk of physical birth abnormalities compared with the general population. Increases the risk of the baby being born smaller than expected compared with the general population.
Zonisamide	Increases the risk of the baby being born smaller than expected compared with the general population. More research is needed to understand whether taking zonisamide during pregnancy increases the risk of having a baby being born with a birth abnormality or a learning or thinking disability.
Other AEDs	Not enough information on their use in pregnancy to make any conclusions about their safety when used during pregnancy.

Brand to generic switching concerns

Concerns about switching between different manufacturers' AED preparations used to treat epilepsy have been raised by patients, patient organisations and prescribers. These include switching between branded and generic products and between generics made by different manufacturers. The main concerns are for AEDs with a narrow therapeutic index and the potentially serious consequences of therapeutic failure. Drug-drug interactions and the relatively low solubility or bioavailability (or both) of some AEDs are other important factors.[9] Different AEDs vary considerably in their characteristics. This influences the risk of whether switching between different manufacturer's products of a particular drug may cause adverse effects, or loss of seizure control.[9] A particular branded preparation may be required to meet the physical needs of specific patients for a particular formulation such as a liquid, sprinkle, granule or a product which is licensed for use in a feeding tube to allow them to take the medication consistently without the need for crushing tablets or adding thickeners. Some people may not be able to take particular manufacturer's preparations because of the excipients they contain for example, ethanol, sorbitol or carbohydrates. Blanket AED switches without individual patient consideration are not recommended.

National guidance

The Commission on Human Medicines (CHM) advised that AEDs are classified into three categories based on therapeutic index, solubility and absorption to help prescribers and patients decide whether it was necessary to maintain continuity of supply of a specific manufacturer's product in the treatment of epilepsy.[9] These three categories are shown in table 2, along with advice for prescribing.

In November 2017, the MHRA added further patient criteria in addition to the three risk-based categories. For AEDs in categories 2 and 3, patient-related factors should be considered when deciding whether it is necessary to maintain continuity of supply for a specific product in the treatment of epilepsy. These include:[10]

- Perception by patients of differences in supply, for example differences in product presentations.
- Co-morbid autism, mental health issues, or learning disability.

The MHRA state that this advice relates only to antiepileptic drug use for the treatment of epilepsy; it **does not apply to their use in other indications** (e.g. mood stabilisation, neuropathic pain). Also stated is that dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that antiepileptic drug. Such cases should be discussed and agreed with both the prescriber and patient (or carer). Where a specific product is not specified, usual dispensing practice can be followed.[9]

NICE [NG217] Epilepsies in children, young people and adults, recommends to follow this MHRA safety advice on switching between different manufacturers' products of a particular antiseizure medication.

Table 2. Advice on switching between different manufacturers' product for the three categories of AEDs[9,10]

Category	Drugs	More details on classification	Advice for prescribing
Category 1	Carbamazepine Phenobarbital Phenytoin Primidone	For these drugs, there are clear indications that clinically relevant differences between different manufacturers' products might occur, even when the pharmaceutical forms are the same and bioequivalence has been shown.	Ensure that the patient is maintained on a specific manufacturer's product.

Category	Drugs	More details on classification	Advice for prescribing
Category 2	Clobazam Clonazepam Eslicarbazepine Lamotrigine Oxcarbazepine Perampanel Rufinamide Topiramate Valproate Zonisamide	Drugs that do not fit into Category 1 or 3.	Base the need for continued supply of a particular manufacturer's product on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history. Take into account patient/carer related factors such as their negative perceptions about alternative products and/or other issues related to the patient should also be taken into account.
Category 3	Brivaracetam Ethosuximide Gabapentin Lacosamide Levetiracetam Pregabalin Tiagabine Vigabatrin	These drugs show all the following characteristics: • High solubility across the relevant range of pHs. • Essentially complete absorption after oral administration. • Dose-response curves for efficacy and safety are not steep. • Therapeutic index is not narrow.	For these drugs, the potential for clinically relevant differences to exist between different manufacturers' products is considered to be extremely low. However, consider other patient/carer-related factors, such as negative perceptions about alternative products and/or other issues related to the patient.

It is recommended that secondary care specialists should provide advice in the 'action for GP' section of the discharge summary or outpatient letter to the GP:

- For AEDs in category 1, the brand name or the generic name plus the name of the generic manufacturer, and the type of formulation, as it is necessary to maintain continuity of supply for a specific product.
- For AEDs in category 2 or 3, the brand name or the generic name plus the name of the generic manufacturer, and the type of formulation if patient factors suggest a particular product is needed.
- If a generic preparation from any manufacturer is suitable for the patient.

The Scottish Intercollegiate Guidelines Network (SIGN) clinical guideline 143 - Diagnosis and management of epilepsy in adults, published in 2018, states that stable dosing with individual antiepileptic formulations (generic or branded) is less likely to be associated with worsening control than changing formulations of individual drugs. They found that some studies suggested that changing between formulations may lead to variations in seizure control and increased utilisation of health resources. Also that formulations of AEDs are not interchangeable and generic substitution should not be routinely made. SIGN 143 recommends that routine switching between different manufacturers of antiepileptic drugs should be avoided.[11]

Antiepileptic withdrawal in epilepsy

Evidence of the risks of seizure recurrence after discontinuation of AEDs was provided by a large, multicentre, randomised, prospective trial of continued antiepileptic treatment versus slow withdrawal

in adults and children with epilepsy who had been seizure free for at least two years. AED withdrawal was associated with an increased risk of seizure recurrence, which was influenced by the duration of seizure freedom, the history of seizure types, the occurrence of one or more seizures after the start of the treatment and whether one, or more than one, AED was being taken. The data from the study were used to develop a prognostic index for seizure recurrence. The higher risks of seizure recurrence with a history of myoclonus reflect the high risk of seizure recurrence following AED withdrawal in juvenile myoclonic epilepsy.[11] When a patient has been seizure free for at least two years, withdrawal of the antiepileptic can be considered, depending on individual circumstances. Carry out an assessment to determine the risk of seizure recurrence and refer to an epilepsy specialist if there is any doubt or concern. There is a risk of seizure recurrence even when patients have been seizure free for several years. If more than one antiepileptic is taken, only one drug should be withdrawn at a time. Reduction in dosage should be gradual over at least three months to prevent rebound seizures. For patients on barbiturates and benzodiazepines, withdrawal should be managed over a longer period to reduce the risk of drug-related withdrawal symptoms. If seizures recur during or after discontinuation of an antiepileptic drug, the last dose reduction should be reversed and guidance sought from an epilepsy specialist.[12] Important factors influencing a decision about AED withdrawal in adults include driving, employment, fear of further seizures, risks of injury or death with further seizures and concerns about prolonged AED treatment.[11] For some people it is also important to consider the impact of AED switches or withdrawal and the impact on driving. The Driver and Vehicle Licensing Agency (DVLA) recommends that patients should not drive during medication changes or withdrawal of antiepileptic drugs, and for 6 months after their last dose. If a seizure occurs due to a prescribed change or withdrawal of epilepsy treatment, the patient will have their driving licence revoked for one year; relicensing may be considered earlier if treatment has been reinstated for 6 months and no further seizures have occurred.[12]

Evidence base

Approval of generic AEDs

Concerns have been raised by some patients and prescribers that bioequivalence criteria might not always be sufficient to ensure equivalent safety and efficacy when switching between different marketed antiepileptic products.[13]

Normally if a generic product is shown to be bioequivalent to the originator or 'reference' product then they can be considered to be clinically equivalent. This is the basis for approval of generic products. The conventional bioequivalence criteria require the 90% confidence interval for the generic/reference product ratio for the mean area under the curve (AUC= plasma drug concentration time) and maximum plasma concentration (Cmax) to lie within the range 80% to 125%. In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90% to 111%. This acceptance interval also applies to Cmax where it is of particular importance for safety, efficacy or drug level monitoring. It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations. Some, but not all, AEDs are considered to be NTIDs.[13,14]

CHM review of switching AEDs

The CHM reviewed spontaneous adverse reactions received by the MHRA (Yellow Card scheme) and publications that reported potential harm arising from switching of AEDs in patients previously stabilised on a branded product to a generic. Following this review, the CHM concluded that reports of loss of seizure control and/or worsening side-effects around the time of switching could be explained as chance, but that a causal link could not be ruled out.[9]

Systematic reviews

A systematic review by Crawford et al published in 2006 explored the potential problems with generic substitution of AEDs.[15] They noted that very few articles described randomised controlled trials (RCTs) comparing generic and branded AED products, most were case reports, letters or opinion pieces. The potential problems with generic substitution included:

- Potentially serious consequences of failure of therapy, particularly in well-controlled patients.
- Potential for adverse events and variability of response to AEDs.
- Need for careful titration and dosing of AEDs and susceptibility of some patients to develop problems, even with small changes in drug levels.
- Bioequivalence, as defined by regulatory bodies, may not correspond to therapeutic equivalence for AEDs, because of the permitted range of bioavailability for generics, evaluation methods that use small numbers of relatively young healthy volunteers and individual variation.
- Potential for problems from poor continuity of supply.
- Cost savings may be outweighed by the cost of adverse consequences.
- Potential medico-legal consequences in patients who did not give informed consent to switching of AEDs.

They recommended that it is prudent for patients, neurologists, and pharmacists to be aware of the potential problems with generic substitution of AEDs and to approve generic prescribing of AEDs for certain high-risk patients prior to it being switched. They considered that it should make little difference to a patient if the initial titration of therapy is with a specific generic product.[15]

The systematic review undertaken by Kesselheim et al assessed seizure outcomes following the use of generic versus branded AEDs. Most of the RCTs were short-term evaluations, but the available evidence did not suggest an association between loss of seizure control and generic substitution of at least three types of AEDs (phenytoin, carbamazepine and valproic acid). Data from six observational studies came to conclusions at odds with nine RCTs about the safety of brand-to-generic switches. This may be explained by factors such as undue concern from patients or physicians about the effectiveness of generic AEDs after a recent switch. Patients with epilepsy can experience significant anxiety with any change to their AEDs. A brand-to-generic switch is likely to cause increased anxiety or worry for many of these patients, which may be a reason for increased clinic visits.[16]

Another systematic review by Yamada et al, concludes that the highest levels of evidence indicate that there should not be a problem with generic substitution, although some patients are more prone to problems with generic products. Some evidence suggests that switches between multiple generic AED products in certain individuals may be problematic – there may be increased use of healthcare resources.[17]

In a further systematic review undertaken by Desmarais et al, the authors noted several case reports and studies which described clinical deterioration and decreased tolerability with generic substitution. Generics did not always lead to the anticipated monetary savings and also raised compliance issues. Although this systematic review is limited by publication bias and heterogeneity of studies, the authors believe there is enough concern to advise generic switching on an individual basis, with close monitoring throughout the transition. Harmful effects of switching patients with epilepsy to generic AEDs have been described especially with valproate, phenytoin, carbamazepine and primidone.[18] Phenytoin, carbamazepine and primidone are all category 1 AEDs where the prescribing advice is to ensure that the patient is maintained on a specific manufacturer's product.[9]

Holtkamp and Theodore reviewed whether generic AEDs were safe or harmful in patients with epilepsy. They concluded that there was sufficient evidence which indicated that most generics are bioequivalent to the originator brand AEDs; they do not pose a relevant risk for patients with epilepsy. However,

some patients are worried about changes in colour and shape of their AEDs which may result in non-adherence. They recommend prescribing a generic AED when a new AED is initiated. Switches from brand to generic AEDs for cost reduction and between generics (for example due to shortages) should be accompanied by thorough counselling of patients on the need for good adherence to reduce risks.[19]

The UK Clinical Pharmacy Association (UKCPA): Neurosciences Group and the Pharmaceutical Market Support Group (PMSG): Generics Sub-Group have developed a consensus view on principles for switching between branded and generic AEDs:[6]

- Only consider switching where there will be a significant clinical, logistical or financial benefit. Risks involved in switching AEDs should be mitigated as far as possible.
- Determine whether the patient has previously experienced problems when switching between brands and generics or if they've 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. Inform patients of the benefits and risks of switching between brands and generics and ask patients their views about switching.
- Patients should not routinely be switched from existing medicines without their consent unless urgent treatment is needed.
- Sustained or Modified Release products present a greater risk and should not be considered generic.
- Patients with highly labile seizure control should not be switched to generics and should be maintained on their usual AED brand or generic.
- Patients with optimal seizure control (i.e. seizure-free or seizure frequency has markedly reduced) should not be switched to generics and should be maintained on their usual brand or generic. This of highest importance where the recurrence of a seizure could lead to socio-economic harm (e.g. loss of a driving licence).
- 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 appropriate.
- 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.
- In summary: Patients identified as suitable for switching from brand to generic are those who agree to try a generic version and take 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.

Cost comparison charts

Cost comparison charts for AEDs are available in the visual data pack accompanying this resource. They show the costs of generic and branded products where generic versions are available in the same formulation as the brand.

Please note that cost comparisons are based on 56 doses and may not directly equate to prescribed doses which are variable. They are a guide to potential cost differences between different preparations. As prices change it is worth checking the latest PrescQIPP cost comparison charts which are updated monthly on the PrescQIPP website for current AED costs.

Switching AEDs

There are a number of branded products which are not due to come off patent for many years, so a switch to a generic is not yet possible. For all switches, the general principles for switching from branded to generic AEDs suggested by the MHRA and UKCPA/PMSG consensus document should be applied.[6,9,10] In addition, table 2 provides advice for prescribing when considering switching between different manufacturers' products.

Consider initiating a generic AED product following recent loss of seizure control where extra (adjunctive therapy) or a new AED will be prescribed (even those where a switch is not recommended).

As with all switches, these should be undertaken in discussion with and agreement of the patient. Blanket switches are not recommended.

Consider informing local community pharmacies in advance of AEDs switches to gain their support for the switch process and to help alleviate potential patient concerns.

Switching category 1 AEDs

Switching category 1 AEDs used to treat epilepsy are not recommended. However, this does not apply when they are used for other non-epilepsy indications.[9] For example, carbamazepine is indicated for trigeminal neuralgia, prophylaxis of bipolar disorder unresponsive to lithium, adjunct in acute alcohol withdrawal, and diabetic neuropathy. Primidone is indicated for essential tremor.[12] A switch to the generic AED may be considered for patients prescribed the AED for these indications. However, currently there are no cost savings in doing so and so these switches are not currently recommended.

Switching category 2 AEDs

Table 3 shows category 2 AED branded products where no generic version is currently available and so switches to less costly generics are not currently possible.[12,20,21]

Table 3. Category 2 AED branded products where no generic version is available[20,21]

Branded product	Generic name	Cost (quantity)
Fycompa® tablets	Perampanel	£140 (28) all strengths
Fycompa® 500micrograms/ml oral suspension sugar free	Perampanel	£127.50 (340ml)
Inovelon® tablets	Rufinamide	£5.15 (10) 100mg £61.77 (60) 200mg £102.96 (60) 400mg
Inovelon® 40mg/ml suspension sugar free	Rufinamide	£94.71 (460ml)
Lamictal® 2mg dispersible tablets	Lamotrigine	£18.81 (30)

Lamotrigine

Savings by switching to generic lamotrigine range from 5% to 98% depending on the strength and formulation of Lamictal®.[12,21] There is currently no generic version of the Lamictal® 2mg dispersible tablets.

The UKCPA/PMSG consensus view is that there is evidence to support switching from Lamictal® to generic lamotrigine; some countries have mandatory switching programmes;[6] the MHRA has issued guidance supporting switching in the UK with some caveats.[9,10]

Sodium valproate

Before considering any brand to generic switches for valproate, first ensure that the new national patient safety advice[7] has been followed for individual patients.

In line with the Drug Safety Update on valproate, healthcare professionals are advised to:[22]

- Continue to follow the existing strict precautions, including that valproate should not be prescribed to female children or women of childbearing potential unless other treatments are ineffective or not tolerated and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP).
- Following a new safety review conducted in light of concerns that the current regulatory requirements for safe use are not being consistently followed, the Commission on Human Medicines (CHM) has advised that there should be greater scrutiny of the way valproate is prescribed and that further risk minimisation measures are required – in particular that two specialists should independently consider and document that there is no other effective or tolerated treatment for patients (male and female) aged under 55 years.
- Consider all other suitable therapeutic options before newly prescribing valproate in patients (male and female) younger than 55 years.
- GPs and pharmacists should continue to provide repeat prescriptions for valproate and dispensers should continue to ensure patients receive the patient card, a copy of the Patient Information Leaflet and packaging bearing pregnancy warnings.
- Patients currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so.

New materials for the Pregnancy Prevention Programme are available. These include a Patient guide, Healthcare Professional Guide, Annual Risk Acknowledgement Form, Risk Acknowledgement Form for male patients starting valproate, Patient card, Pharmacy poster, Warning stickers, Product Information and patient information leaflet There is also a video available to support healthcare professionals.[23]

These regulatory changes are further supported by:

- Smaller pack sizes to encourage monthly prescribing
- A pictogram/warning image on valproate labelling
- Rules introduced in 2023 to ensure all patients receive the whole pack of valproate with the warnings on the box.[24]

Integrated Care Boards (ICBs) (in England), Health Boards (HBs) in Scotland and Wales, and Health and Social Care Trusts (in Northern Ireland) were required to take action in response to the valproate National Patient Safety Alert by 31 January 2024. These actions were to:

1. Designate a new or existing group to co-ordinate the implementation of the new regulatory measures in providers, with oversight from a senior quality group. This group should include (but is not restricted to):
   a. An appointed chair with delegated responsibility for the actions in this alert.
   b. Representation from clinical leads in all the specialities named above and any other relevant departments.
   c. A mechanism by which the group can involve and be informed by patients with lived experience.
2. The group should be tasked with, and document, progress towards:
   a. Updating all local guidance and protocols relating to prescribing of valproate to reflect the new regulatory position, including definitions of the roles and responsibilities of clinicians and provider organisations, and the recording of compliance with the risk forms.

b. Commissioning work if necessary to understand the needs of the affected population, including those people most at risk of health inequalities.
c. Reviewing the results of local audit(s) of compliance with the existing PPP measures for girls and women of childbearing potential prescribed valproate.
d. Commissioning/determining the local pathways of care for women of childbearing potential and girls in relation to the prescribing and review of valproate.
e. Planning for and identification of clinical resource to meet the identified needs of the population and implement the new regulatory measures.

3. Based upon the findings of the above, the group should produce an Action and Improvement Plan by the alert deadline that is communicated with all relevant staff to ensure smooth implementation of the new regulatory measures and to allow for continuous improvement in care of patients who are considering or being prescribed valproate, including ongoing improvement, monitoring and audit.[7]

The MHRA issued an update on a new study on the outcomes in children whose fathers took valproate at the time of conception commissioned by the European Medicines Agency, which was resubmitted after repeat analysis by the researchers. The resubmitted study is being reviewed and any further guidance will be communicated to patients and healthcare professionals as soon as possible. As a precaution, male patients on valproate who are planning a family in the next year should talk to their healthcare professional about their treatment.[25]

To support implementation of the MHRA and CHM new recommendations for valproate in anyone under the age of 55 with reproductive capacity, the Association of British Neurologists has produced clinical guidelines for valproate prescribing in adult (16 and over) neurology.

For patients continuing to receive valproate after being reviewed in line with national patient safety advice, switches to generics or less costly brands can then be considered.[7]

The cost of generic sodium valproate compared to brand Epilim® is currently less costly for only the 500mg gastro-resistant tablets.[20] As Drug Tariff prices fluctuate this may change in the future so visit the PrescQIPP cost comparison charts on the PrescQIPP website for current prices. Table 4 illustrates the savings by switching from Epilim® brand preparations.

Table 4. Potential sodium valproate switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Epilim® 500mg gastro-resistant tablets	Sodium valproate 500mg gastro-resistant tablets	£0.63	4%
Epilim Chronosphere®1000mg	Episenta® 1000mg	£33.04	59%
Epilim Chronosphere® 500mg MR granule	Episenta® 500mg MR granule sachets	£33.04	79%
Epilim® Chrono 300 controlled release tablets	Epival® CR 300mg tablets	£3.43	40%
Epilim® Chrono 500 controlled release tablets	Epival® CR 500mg tablets	£5.71	35%

The UKCPA/PMSG consensus document states that a cautious switching policy (within the salt) is supported by scanty evidence.[6]

Topiramate

Topiramate switch savings range from £12.44 to £369.18 per 56 doses. The UKCPA/PMSG consensus document states that limited evidence would suggest cautious switching in appropriate patients.[6] Table 5 illustrates the potential topiramate switch savings.

Table 5. Potential topiramate switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Topiramate 50mg/5ml oral suspension SF	Topamax® 50mg sprinkle capsules	£369.18	92%
Topiramate 100mg/5ml oral suspension SF	Topamax® 50mg sprinkle capsules	£243.96	78%
Topamax® 200mg tablets	Topiramate 200mg tablets	£73.77	72%
Topamax® 100mg tablets	Topiramate 100mg tablets	£43.27	82%
Topamax® 50mg tablets	Topiramate 50mg tablets	£19.61	66%
Topamax® 25mg tablets	Topiramate 25mg tablets	£12.44	69%

Oxcarbazepine

Oxcarbazepine (Category 2 AED) is the 10-keto analogue of carbamazepine (a category 1 AED) but has a distinct pharmacokinetic profile.[26] The UKCPA/PMSG consensus document states that limited studies indicate a greater variability in blood levels with this agent. In these circumstances switching is not supported.[6] This should be taken into account should a switch from Trileptal® to generic oxcarbazepine be considered. However, it is a Category 2 AED and so a switch should be possible if MHRA guidance for the switch is adhered to.[9,10] New patients may be initiated and stabilised on generic oxcarbazepine. Table 6 illustrates the oxcarbazepine potential switch savings.

Table 6. Potential oxcarbazepine switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Trileptal® 300mg tablets	Oxcarbazepine 300mg tablets	£20.18	74%
Trileptal® 600mg tablets	Oxcarbazepine 600mg tablets	£11.48	21%

Eslicarbazepine

Whilst generic versions of eslicarbazepine tablets are available, they are currently the same cost as the brand Zebinix®. There are currently no generic versions of Zebinix® 50mg/1ml oral suspension sugar free. A branded generic Arupsan® is available as 200mg and 800mg tablets but they are currently only 1p difference per pack compared to Zebinix® brand, see table 7.

Table 7. Potential eslicarbazepine switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Eslicarbazepine generic/ Zebinix® 200mg tablets	Arupsan® 200mg tablets	£0.01	0.02%
Eslicarbazepine generic/ Zebinix® 800mg tablets	Arupsan® 800mg tablets	£0.01	0.03%

Clobazam

Clobazam is a schedule 4 part 1 controlled drug and so is subject to minimal control in that controlled drug prescriptions requirements, safe custody requirements and records in registers do not apply.[12] The UKCPA/PMSG consensus states that 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.[6] Generic clobazam tablets and oral suspensions are currently more expensive than branded

versions Frisium®, Zacco® and Perizam®. The largest cost saving of £95.70 per 56 doses is achieved by switching from Clobazam 5mg/5ml oral suspension to Zacco® 5mg/ml oral suspension. Refer to table 8 for other potential savings.

Table 8. Potential clobazam switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Clobazam 5mg/5ml oral suspension sugar free	Zacco 5mg/5ml oral suspension	£95.70	53%
Clobazam 10mg/5ml oral suspension sugar free	Zacco® 10mg/5ml oral suspension	£92.36	50%
Perizam 2mg/ml oral suspension	Zacco 10mg/5ml oral suspension	£84.93	48%
Perizam® 1mg/ml oral suspension	Zacco® 5mg/5ml oral suspension	£84.00	50%
Clobazam 20mg tablets	Frisium® 10mg tablets x2	£8.83	49%
Clobazam 10mg tablets	Frisium® 10mg tablets	£3.04	39%

Zonisamide

The UKCPA/PMSG consensus states that zonisamide is not a theoretical high risk and that 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.[6] The largest cost saving of £46.90 per 56 doses is achieved by switching from Zonegran® 100mg capsules to generic zonisamide 100mg capsules.[20,21] Refer to table 9 for other potential savings.

Table 9. Potential zonisamide switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Zonisamide 25mg capsules	Zonegran® 25mg capsules	£12.40	26%
Zonegran® 100mg capsules	Zonisamide 100mg capsules	£46.90	75%
Zonegran® 50mg capsules	Zonisamide 50mg capsules	£34.32	73%

Switching category 3 AEDs

For all switches, the general principles for switching from branded to generic AEDs suggested by the MHRA and UKCPA/PMSG consensus group should be applied.[6,10] Table 2 provides advice for prescribing when considering switching between different manufacturers' products.

Table 10 shows category 3 AED branded products where no generics are available and so prescribing is by brand name.[20,21]

Table 10. Category 3 AED brands with no generic available[20,21]

Branded product	Medicine	Cost (quantity)
Briviact® tablets	Brivaracetam	£34.64 (14) 10mg £129.64 (56) 25mg, 50mg, 75mg, 100mg
Briviact® 10mg/ml oral solution		£115.83 (300ml)
Gabitril® tablets	Tiagabine	£52.04 (100) 5mg £104.09 (100) 10mg £156.13 (100) 15mg
Kigabeq®	Vigabatrin	£66.47 (100) 100mg soluble tablets SF £148.72 (50) 500mg soluble tablets SF
Sabril® tablets/powder	Vigabatrin	£24.60 (50) 500mg sachets SF £44.41 (100) 500mg tablets

Levetiracetam

New patients should be initiated on generic levetiracetam. The UKCPA/PMSG consensus states that 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.[6] Table 11 illustrates that the largest cost saving of £84.32 per 56 doses is achieved by switching from Keppra® 1g tablets to generic levetiracetam 1g tablets.

Table 11. Levetiracetam potential switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Keppra® 1g tablets	Levetiracetam 1g tablets	£84.32	95%
Keppra® 750mg tablets	Levetiracetam 750mg tablets	£75.36	96%
Keppra® 100mg/ml oral solution	Levetiracetam 100mg/ml oral solution SF	£45.14	72%
Keppra® 500mg tablets	Levetiracetam 500mg tablets	£43.47	94%
Keppra® 250mg tablets	Levetiracetam 250mg tablets	£24.34	93%

Pregabalin

New patients should be initiated on generic pregabalin where appropriate. Pregabalin is a Schedule 3 Controlled Drug and prescription lengths are strongly recommended not to exceed 30 days.[12] The UKCPA/ PMSG consensus states that most use of pregabalin is in neuropathic pain where the dose is less critical than in epilepsy.[6] The largest cost saving of £94.63 per 56 doses (98% saving) is achieved by switching from Lyrica® 50mg capsules to generic pregabalin 50mg capsules. Switching from tablet formulations to generic capsules across the range of strengths offers savings between 57% and 71%. Savings arising from switching from different brands, strengths and formulations of pregabalin to generic pregabalin capsules range from 57% to 98%.[20,21] Table 12 illustrates these potential savings.

Table 12. Pregabalin potential switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Alzain® 25mg capsules	Pregabalin 25mg capsules	£2.01	40%
Axalid® 25mg capsules	Pregabalin 25mg capsules	£16.97	85%
Lyrica® 25mg capsules	Pregabalin 25mg capsules	£61.42	95%
Alzain® 50mg capsules	Pregabalin 50mg capsules	£3.72	62%
Axalid® 50mg capsules	Pregabalin 50mg capsules	£17.68	89%
Lyrica® 50mg capsules	Pregabalin 50mg capsules	£94.63	98%
Alzain® 75mg capsules	Pregabalin 75mg capsules	£3.16	53%
Axalid® 75mg capsules	Pregabalin 75mg capsules	£17.12	86%
Lyrica® 75mg capsules	Pregabalin 75mg capsules	£61.57	96%
Alzain® 100mg capsules	Pregabalin 100mg capsules	£1.81	39%
Axalid® 100mg capsules	Pregabalin 100mg capsules	£17.10	86%
Lyrica® 100mg capsules	Pregabalin 100mg capsules	£93.75	97%
Alzain® 150mg capsules	Pregabalin 150mg capsules	£3.32	47%
Axalid® 150mg capsules	Pregabalin 150mg capsules	£16.28	82%
Lyrica® 150mg capsules	Pregabalin 150mg capsules	£60.73	94%
Alzain® 200mg capsules	Pregabalin 200mg capsules	£2.52	42%
Axalid® 200mg capsules	Pregabalin 200mg capsules	£16.48	83%
Lyrica® 200mg capsules	Pregabalin 200mg capsules	£60.93	95%
Alzain® 225mg capsules	Pregabalin 225mg capsules	£4.00	50%
Axalid® 225mg capsules	Pregabalin 225mg capsules	£15.96	80%
Lyrica® 225mg capsules	Pregabalin 225mg capsules	£60.41	94%
Alzain® 300mg capsules	Pregabalin 300mg capsules	£4.07	45%
Axalid® 300mg capsules	Pregabalin 300mg capsules	£15.03	75%
Lyrica® 300mg capsules	Pregabalin 300mg capsules	£59.48	92%

Gabapentin

Gabapentin is a Schedule 3 Controlled Drug and prescription lengths are strongly recommended not to exceed 30 days.[12] The UKCPA/PMSG consensus states that there are no specific data to suggest that switching causes problems in clinical practice. There is no consistent evidence to suggest that switching to a generic is any worse that switching within brand. In these circumstances it seems reasonable to allow switching for most patients in line with MHRA guidance. Most gabapentin use is for neurological pain so the dose is not critical.[6,10] The largest cost saving of £41.93 for 56 doses is achieved by switching from to branded Neurontin® 600mg tablets to generic gabapentin 600mg tablets.[20,21] Savings arising from switching from Neurontin® capsules or tablets to generic gabapentin capsules or tablets range from 73% to 95%. Table 13 illustrates these savings.

Table 13. Gabapentin potential switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Neurontin® 800mg tablets	Gabapentin 800mg tablets	£39.88	73%
Neurontin® 600mg tablets	Gabapentin 600mg tablets	£41.93	88%
Neurontin® 400mg capsules	Gabapentin 400mg capsules	£25.77	94%
Neurontin® 300mg capsules	Gabapentin 300mg capsules	£22.47	95%

Lacosamide

The UKCPA/PMSG consensus states that 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.[6]

Whilst Eplaid® brand is less costly than the Vimpat® brand, generic versions of lacosamide are the least costly for all strengths apart from the 150mg tablets where Eplaid® 150mg tablets are the least costly preparation for this strength. Table 14 illustrates that the largest cost saving of £132.98 for 56 doses is achieved by switching from to branded Vimpat® 200mg tablets to generic lacosamide 200mg tablets.[20,21] Table 14 illustrates the lacosamide potential switch savings.

Table 14. Lacosamide potential switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Vimpat® 200mg tablets	Lacosamide 200mg tablets	£132.98	92%
Eplaid® 200mg tablets	Lacosamide 200mg tablets	£89.73	89%
Vimpat® 100mg tablets	Lacosamide 100mg tablets	£79.53	92%
Eplaid® 100mg tablets	Lacosamide 100mg tablets	£53.58	88%
Vimpat® 50mg tablets	Lacosamide 50mg tablets	£36.96	85%
Eplaid® 50mg tablets	Lacosamide 50mg tablets	£24.00	79%

Ethosuximide

The UKCPA/PMSG consensus states that 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.[6]

Emeside® 250mg/5ml syrup and 250mg capsules and Epesri® 250mg capsules are less costly than the current generic ethosuximide oral solutions and capsules available. Table 15 illustrates these savings. As Drug Tariff prices change it is worth checking the PrescQIPP cost comparison charts for current costs.

Table 15. Ethosuximide potential switch savings[20,21]

Switch from	Switch to	Saving per 56 doses	Saving %
Ethosuximide 250mg/5ml oral solution sugar free	Emeside® 250mg/5ml syrup	£124.18	49%
Ethosuximide 250mg/5ml oral solution	Emeside® 250mg/5ml syrup	£114.20	47%
Ethosuximide 250mg capsules	Emeside® or Epesri® 250mg capsules	£110.26	52%

AEDs with no categorisation

Cenobamate/Stiripentol

Cenobamate and stiripentol were not included in the MHRA review of antiepileptic drugs as they were not available at the time of the review.[9,10] Therefore, there is no categorisation available for these drugs. Currently only the brand versions, Ontozry®/ Diacomit® are available and so no switches to a generic are currently possible.[20,21]

Sultiame/ Felbamate

These products are only available as either special order or import products.[21] They were not included in the MHRA review of antiepileptics drugs and so have no categorisation available.[9,10]

Cost and savings

Approximately £376 million is spent annually on AEDs across England, Wales, Scotland, Northern Ireland and Isle of Man (NHSBSA Oct – Dec 2023 and Public Health Scotland Aug – Oct 2023). Table 16 illustrates the annual spend on AEDs by country.

Table 16. Spend on AEDs in England, Wales, Northern Ireland, Isle of Man and Scotland (NHSBSA Oct-Dec23, Public Health Scotland Aug-Oct23)

	AEDs annual spend	AED spend per 100,000 population
England	£300,752,476	£477,009
Wales	£19,653,269	£597,645
Northern Ireland	£17,338,031	£846,799
Isle of Man	£431,286	£483,559
Scotland	£37,774,672	£633,316

The cost differential between originator brand AEDs and generic AEDs is significant for many drugs. Refer to tables 4 to 15 and the PrescQIPP cost comparison charts for more details.

In most cases, commencing new patients on generic AEDs would provide better value for money for the NHS as a whole. **Appropriately switching 30% of patients on selected AEDs to their generic counterpart or to less costly branded AEDs could produce significant financial savings of around £21million annually or £28,773 per 100,000 population without impacting on AED efficacy or patient safety.** These savings can be used to fund alternative AEDs where needed or other NHS services for patients with epilepsy or other NHS services required for patients.

Any switch programme should take into account the MHRA and UKCPA/MPSG consensus advice on switching between different manufacturers' products for the three categories of AEDs.[6,10] Blanket switches are not recommended.

Table 17 summarises the 12 month savings available by switching 30% of patients to generic AEDs or less costly branded AEDs in England, Wales, Scotland, Northern Ireland and Isle of Man for the AED switches outlined in this bulletin. The PrescQIPP visual data pack accompanying this resource can be viewed for organisation specific prescribing and savings data.

Table 17. AED switch savings for England, Wales, Scotland, Northern Ireland and the Isle of Man (NHSBSA Oct-Dec23, Public Health Scotland Aug-Oct23)

AED switch	AED category	12-month potential saving for 30% switch	12 month saving potential for 30% switch per 100,000 population
Lamictal® to lamotrigine	2	£5,498,070	£7,386
Epilim® to sodium valproate, Episenta® or Epival®	2	£1,784,117	£2,397
Topamax® to topiramate	2	£834,722	£1,121
Trileptal® to oxcarbazepine	2	£77,337	£104
Clobazam to Frisium®/Zacco/Perizam®	2	£2,161,514	£2,904
Zonegran® to zonisamide	2	£542,334	£729
Keppra®/Desitrend® to levetiracetam	3	£6,008,111	£8,071
Lyrica®/Alzain®/Axalid®/Lecaent to pregabalin or pregabalin tablets to pregabalin capsules	3	£998,060	£1,341
Neurontin® to gabapentin	3	£186,396	£250
Vimpat® to lacosamide	3	£571,064	£767
Ethosuximide to Emeside®/Epesri®	3	£2,757,064	£3,704
Total		£21,418,790	£28,773

Summary

Secondary care specialists should provide advice in the 'action for GP' section of the discharge summary or outpatient letter to the GP whether a generic AED preparation is suitable for the patient or whether a particular generic manufacturer or brand is necessary.

The MHRA sets out advice on switching between different manufacturers products for the three categories of AEDs.[10] This advice and the UKCPA/PMSG consensus advice on points to consider when switching should be followed when considering switching branded AEDs to generic AEDs.[6]

Any switch to a generic AED should be fully discussed with the patient to gain their agreement with the switch, reduce the risks of nonadherence and anxiety caused by the switch.

All patients taking AEDs for non-epilepsy indications can be considered for a generic AED switch discussed with the patient in advance.

Across England, Wales, Scotland, Northern Ireland and the Isle of Man, savings of approximately £21 million annually could be realised by appropriately switching 30% of selected AEDs to generic or less costly branded AEDs.

Patient resources

NHS. Treatment. Epilepsy. https://www.nhs.uk/conditions/epilepsy/treatment/

Epilepsy Action. Switching between different versions of epilepsy medicine. https://www.epilepsy.org.uk/info/treatment/anti-seizure-medication/switching-between-different-versions-of-epilepsy-medicine

Epilepsy Society. Generic and branded anti-seizure medications. https://epilepsysociety.org.uk/about-epilepsy/anti-seizure-medication/generic-branded

Patient Guide: What you need to know about valproate

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-348-antiepileptic-drugs/
Implementation tools	
Data pack	https://data.prescqipp.info/views/B348_Antiepilepticdrugs-appropriateswitching-togenericsorbrandequivalents/FrontPage?%3Aembed=y&%3Aiid=1&%3AisGuestRedirectFromVizportal=y

Information compiled by Karen Homan, PrescQIPP CIC, March 2024 and reviewed by Katie Smith, PrescQIPP CIC, April 2024. Non-subscriber publication April 2025.

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