Epilepsy: new MHRA drug safety advice on switching between anti-epileptic products

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The MHRA has issued new advice about oral anti-epileptic drugs (AEDs) and switching between different manufacturers’ products of a particular drug.

Following a review of the available evidence, the Commission on Human Medicines (CHM) has advised that there is a need to maintain continuity of supply of a specific product for some AEDs, but not all. AEDs have been classified into 3 categories depending on the level of potential concerns related to switching between different manufacturers’ products.

The NICE guideline on The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care now links to the MHRA advice.

Background

When a generic medicinal product is shown to be bioequivalent to the originator (‘reference’) product, as defined by the relevant regulations and guidelines, it follows that the products can be considered to be clinically equivalent. However, concerns about switching between different manufacturers’ products of anti-epileptic drugs (AEDs) have been raised by patients and prescribers. These include switching between branded originator and generic products, and between different generic products of a particular drug. The main reasons for these concerns are the narrow therapeutic index of some AEDs 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.

Potential risk from switching between different manufacturers’ products

The CHM reviewed spontaneous adverse reactions received by the MHRA, and publications that reported potential harm arising from generic switching of AEDs in patients previously
stabilised on a branded product. Following this review, the CHM concluded that reports of loss of seizure control and/or worsening of side effects around the time of switching between products could be explained as chance associations, but that a causal role of switching could not be ruled out in all cases.

New Categorisation to help minimise risk

The CHM considered the characteristics of AEDs and advised that they could be classified into 3 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. These categories are listed below:

- **Category 1** – Phenytoin, carbamazepine, phenobarbital, primidone. For these drugs doctors are advised to ensure that their patient is maintained on a specific manufacturer’s product.
- **Category 2** – Valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate. For these drugs the need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with patient and/or carer taking into account factors such as seizure frequency and treatment history.
- **Category 3** - Levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin. For these drugs it is usually unnecessary to ensure that patients are maintained on a specific manufacturer’s product unless there are specific concerns such as patient anxiety, and risk of confusion or dosing errors.

Advice for healthcare professionals

- Different AEDs vary considerably in their characteristics, which influence the risk of whether or not switching between different manufacturers’ products of a particular drug may cause adverse effects or loss of seizure control.
- AEDs have been divided into 3 categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer’s product.
- If it is felt desirable for a patient to be maintained on a specific manufacturer’s product this should be prescribed either by specifying a brand name or by using the generic drug name and name of the manufacturer (otherwise known as the ‘Marketing Authorisation Holder’).
- This advice relates only to AEDs used for treatment of epilepsy and does not apply to the use of AEDs for indications such as mood stabilisation or neuropathic pain.

Additional advice for pharmacists

- 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 AED. Such cases should be discussed and agreed with both the prescriber and patient (or carer).
- Usual dispensing practice can be followed when a specific product is not stated.
NICE guidance on AEDs

NICE guidance on the diagnosis and management of the epilepsies in adults and children in primary and secondary care (Clinical Guideline 137) contains the following statement with regard to the need for continuity of supply:

‘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) on the bioavailability and pharmacokinetic profiles of individual AEDs, but note that these do not give information on comparing bioavailability of different generic preparations.’

NICE advice to healthcare professionals in the epilepsy guideline now links to the MHRA advice.

In addition to the NICE guideline on epilepsy, see the NICE Evidence topic page and the NICE Clinical Knowledge Summary on epilepsy for a general overview of the condition. The NICE Pathway: epilepsy brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

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