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AUSTRALIAN EPILEPSY ASSOCIATIONS

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29 March 2010

Submission on behalf of Joint Epilepsy Council of Australia and Epilepsy Australia

Epilepsy Australia is the national coalition of state-based community associations working to improve the lives of people with epilepsy and their families. Epilepsy Australia is an associate member of the International Bureau for Epilepsy.

Epilepsy Australia thanks the Committee for the opportunity to present information and evidence regarding an important, indeed urgent, matter regarding generic medicines and their place in the treatment of epilepsy. On this basis, this document specifically addresses the issues relating to the following topic in the Inquiry:

b) The criteria and clinical evidence used to qualify drugs as interchangeable at a patient level

Since the introduction of generic medicines to the Australian public via the Pharmaceutical Benefits Scheme there has been considerable disquiet expressed by many people involved with epilepsy care, including clinicians, community-based associations and people with epilepsy themselves. This disquiet has generally been dismissed by those in favour of generic substitution as having no evidence base or having a low evidence base in terms of Evidence-based Medicine guidelines. However, that has not assisted those who have been adversely affected by the switching of their medicines to a generic one.

The case studies below illustrate some of the problems we will discuss further:

Client one

19 year old male with intellectual disability taking Brand name medication for Generalised Tonic Clonic seizures. Client had good seizure control. GP changed prescription to allow generic substitution. Mother filled script and Pharmacist asked her if she wanted the cheaper version; she said 'of course' not knowing the possible complications. After taking the generic form of medication for about two weeks, the male client started showing aggressive behaviour. Family consulted a doctor who referred them to behavioral specialists. This lasted 6 months. The family contacted the state-based community organisation to discuss the matter as they suspected the medication was to blame. It was suggested they go back to the brand name medication the client had used previously. They did this and within two weeks the behaviour normalized and they stated "we have our son back".

Client two

Single, 40 year old male with cognitive impairment receiving a disability pension had his branded antiepileptic medication of seven years changed to a generic formulation with the promise at the pharmacy it would save him a few dollars. The generic formulation differed from his branded AED in colour (purple) and was the same shape, colour (white) and size as his antidepressant medication. In his confusion he overdosed accidentally on the antidepressant thinking he was taking his antiepileptic medication, while he missed taking his AED for several days. While the outcome was that he was confused and increasingly

cognitively impaired for four days it could have been catastrophic. Not understanding what was happening he sought advice from his epilepsy counselor who was able to identify the problem and have his original branded medication re-prescribed.

Client three

19 year old male client on brand name medication for Generalised Tonic Clonic seizures which were well controlled. Changed to generic brand and started having breakthrough seizures once per fortnight. He lost his license as a result of the increased seizures and consequently his job was in jeopardy. A neurologist advised him to go back to the brand name and if seizures continue to increase medication. At this point the client phoned the state-based community organisation to find out the difference between generics and brand names. Within 2 weeks of taking the brand name at the same dose, his seizures became less and after 2 months he was seizure free.

Client four

A child was taking brand name medication until the family changed to generic medication on the recommendation of the pharmacist. The child started to feel sick all the time and very tired. The family rang the state-based community organisation to see if they did right thing changing medication. It was suggested they discuss the strategy of going back to the brand name with their GP. Following the return to the brand name medication the child was feeling better within a week.

The issues that these case studies highlight are:

- That generic Anti-Epileptic Drugs (AED) cannot be substituted for brand name AEDs as a matter of course;
- The view that there is no difference between brand names in terms of toxicity and bioavailability (that is the active ingredient is the same) is misleading and results in disastrous consequences for individuals and their families;
- There is too little information available to people with epilepsy and their families on the possible implications of such substitution.

That generic Anti-Epileptic Drugs (AED) cannot be substituted for brand name AEDs as a matter of course:

The Epilepsy Society of Australia (ESA) states in its Position Statement on Generics (<http://www.epilepsy-society.org.au/pages/guidelines2.php>):

“Most antiepileptic drugs (AEDs) have a narrow therapeutic index. Dosage adjustment is required to provide optimal seizure control while avoiding adverse drug effects. The titration of dose of AEDs is guided by target dose, plasma drug concentration reference range or seizure response. The first two of these three factors are determined from population studies of treated patients. In the individual patient the range of effective and tolerable AED dose or plasma drug concentration is often not known.”

The ESA continues:

“Case reports and retrospective studies indicate that there is a risk of loss of seizure control or toxicity if interchange of generic and innovator AED occurs. Crawford et al. (1996) surveyed 2,285 patients with epilepsy and obtained responses from 1333. Of the patients responding 251 reported that their AED brand (either carbamazepine, sodium valproate or phenytoin) had been switched with 74 noting increase in seizure frequency or adverse events. Of these patients the investigators considered 27 were due to the switching of brand.”

This is not an isolated position. The United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines on epilepsy state that switching between formulations or brands of AEDs is not recommended (www.nice.org.uk/CG020). In addition, the UK National Health Services Choices website (www.nhs.uk) suggests AEDs be prescribed by brand, to ensure patients receive consistency in the active ingredient.

The National Society for Epilepsy in the UK has argued to the UK Dept of Health that:

“Branded and generic versions of the same AEDs are expected to have the same levels of active ingredient. The non-therapeutic contents of the drugs (the excipients), however, can be very different, and these affect

the bioavailability of the drug and can vary its therapeutic effect by up to 50 per cent. The excipients may vary in different generic versions of a drug, and from the original brand name version. In a worst case scenario somebody who took their prescription for a generic AED to different pharmacists over a period could end up with a range of different generics being prescribed - all with different formulations - potentially causing havoc to their seizure control and leading to substantial risks.”

<http://www.epilepsysociety.org.uk/NewGetInvolved/Awarenessraising/Countepilepsyoutcampaign/ReporttotheDoH>

In France, Germany and Italy, professional and community organisations hold similar concerns and policies.

In the United States there is published evidence of the problems related to generic substitution. For example, Berg et al (Generic substitution in the treatment of epilepsy: Case evidence of breakthrough seizures. *Neurology* 2008; 70; 525) found through a large survey of physicians' case studies that breakthrough seizures resulted from generic substitution.

Based on this level of evidence the United State Epilepsy Foundation argues that:
‘Recent literature reviews document consistent international opinion that despite existing regulatory criteria to ensure the bioequivalence of generic versions of anti-epileptic therapeutic agents, a small but significant number of people with epilepsy continue to experience adverse reactions when switching. Recent studies confirm that for those people who experienced adverse reactions, the level of medication in their blood was dramatically different, even while on reputedly equivalent products. Other studies document a significantly higher rate of emergency room visits by people following a switch in medications, and the “switch-back” rates of anti-epileptic products (that is, individuals being returned to their previous product under a physician’s guidance) is a great deal higher than in other drug products.’

<https://epilepsyfoundation.org/advocacy/care/genedrev.cfm>

The American Epilepsy Society, representing US neurologists essentially holds views similar to the Australian Society for Epilepsy and argues for further research.

<http://www.aesnet.org/index.cfm?objectid=77B10758-E7FF-0F41-2C82BE234AB8CD24>

The view that there is no difference in bioequivalence between brand and generic AEDs results in disastrous consequences for people with epilepsy and their families;

As we have seen from the above case studies people are likely to lose their driving licences, possibly their employment, miss school or be unable to complete schoolwork and possibly also lose their health. The claim that generics are the same as brand names in the case of AEDs is misleading as it does not provide the full information that there is a potential for breakthrough seizures. There are hidden personal costs associated with this lack of information. People do not associate the change in their health with the change in their AEDs. Consequently they seek other explanations first, including more diagnostic tests, further physician consultations or allied health consultations. These also are related to costs to the health system which far outweigh the savings by switching to generic AEDs.

Because of the disastrous effects on people with epilepsy, The New York State Assembly has recently passed a bill which prohibits a pharmacist from substituting any anti-epileptic drug for the prescribed anti-epileptic drug without notification of and the informed consent of the prescriber and patient or such patient's parent, guardian or spouse.

<http://www.assembly.state.ny.us/leg/?bn=S05855&sh=t>

There is too little information on the possible implications of substitution;

The lack of information means that when people with epilepsy and their families are presented with the chance to make savings by switching to generics they do so by trusting in the pharmacist's expertise, or the pharmacist's proxy, the pharmacy assistant. However, while the pharmacist is an expert in dispensing, s/he is making an offer that is not based on pharmacological expertise but to save costs and because the Government promotes generics and rewards community pharmacies for actively promoting generics. All people with chronic illnesses require adequate information on which to base their decisions and it is clear that the decision to switch to generic AEDs is a more serious decision than just saving money.

Other issues related to a lack of information are that not all generics are the same.

- Different pharmacists carry different generics and one generic may be substituted for another, taking the person even further away from the original therapeutic equivalent;

- Variations in the size, shape and colours and packaging are confusing leading some people to believe they are taking different medicines or in the case of those with cognitive impairment leading to even greater confusion.
- An important issue relates to the influence of Government promotion of generics on health professionals' attitudes to generic AEDs. Health professionals may be ill-informed of the current debates. Because people's experience of generic substitution is regarded as 'anecdotal' or not important there is less regard to informing people with epilepsy about generics policy or that they have a right to refuse them.

Epilepsy Australia submits to this Inquiry:

- Epilepsy Australia supports the position of Epilepsy Society of Australia that when a person has achieved good control on a brand name AED they should not change to a generic or even another brand name AED. Any change should be under the direction of the treating doctor who will monitor the situation and not under the direction of a community pharmacist, or in many cases the pharmacist's assistant, who suggests it in a 'five second consult' over a counter.
- The overall problem relates to any switching from one AED to another. This may lead to breakthrough seizures or other health-related problems. However, the most usual switching is from brand name AEDs to generics, hence this aspect must be recognised.
- AEDs must be exempted from current policies regarding generics with GPs and pharmacists understanding that it is unsafe to dispense any version of AEDs different from the one the patient normally takes. In fact guidance needs to be issued to explain that this is unacceptable and highly risky practice.
- Tick boxes on prescription forms are not a safe means of prescribing and are often ignored.
- While evidence suggests that it may only be a small number of people with epilepsy who are adversely affected by this level of substitution this should not be an argument for not providing all people with epilepsy and their families with relevant information. Nearly all consumer medicine information offers information on possible though rare adverse effects in common medicines.
- The proposition that since there is no firm evidence that generics create breakthrough seizures or other health problems then there is no need to forewarn people of potential problems does not hold. Equally, there is an argument that enough evidence exists to suggest further research is worthwhile.
- In the meantime, while awaiting for such research and its results, it is valid to argue that it is better the Government err on the side of safety and promote the view that people with well-controlled epilepsy SHOULD NOT switch to generics.
- Epilepsy Australia expects the Government to actively promote that more information be provided to people with epilepsy and to health professionals on possible side effects.

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