

Weighing up the costs of switching AEDs

How many times have we been asked by the pharmacist would we prefer the cheaper brand if available? Almost every time we get a prescription filled. The chance to save a few dollars is very appealing, especially when there are several prescriptions being dispensed at the same time, but are we making an informed decision. Are generic drugs as safe and effective as the original brands?

Why generics?

The development of any new drug is extremely costly as it can take a decade to be rigorously tested and evaluated before it is approved for manufacture and distribution.

To help recoup this enormous investment, the pharmaceutical company that developed the drug has the sole rights, or patent, to manufacture and distribute the drug under its chosen name for a determined amount of time under the law. This is how brand names become well known and trusted.

When the patent expires, so do these exclusive rights. Other pharmaceutical companies are able to produce their own version, or generic formulation, of the drug, market it under a different name and, without the cost of development, at a cheaper price.

Are the drugs the same?

For a generic drug to enter the market, its manufacturer must successfully demonstrate to the Therapeutic Goods Authority (TGA) that the generic drug has similar absorption, distribution, metabolism and excretion rates as the branded drug, in other words it is bioequivalent to the original, before it can be produced and marketed, and considered for listing on the Pharmaceutical Benefits Scheme (PBS).

During the manufacturing process the active ingredients of the generic drug remain the same as the original, but the inactive ingredients such as lactose, dyes and gluten will be slightly different, changing the physical components of the medicine. These may include the shape, colour or texture of the drug.

For the majority of medicines, changes to these inactive ingredients do not alter overall bioequivalence and it is deemed a safe substitute for the branded drug. A common example is painkilling medicines.

But for some drugs, even subtle changes in the inactive ingredients may have significant effects. These drugs, which include antiepileptic drugs (AEDs), are described as having a *narrow therapeutic window* – that is the range between the lowest dose that has a positive effect (controlling seizures) and the highest dose before the side effects (toxicity, and/or increase in seizure

activity) outweigh the benefits of the drug, is quite narrow.

Neurologists specializing in the treatment of epilepsy have raised concerns as to whether standard bioequivalence testing for AEDs is rigorous enough.

In standard bioequivalence testing, the two drugs being compared are deemed bioequivalent if the tests show that they are statistically less than 20% different.

Given the narrow therapeutic window in AEDs, a 20% difference between how the drug works in the body has the potential to cause side effects. If the generic formulation has 20% greater absorption than the branded drug, it has the potential to produce a toxic effect. If the generic has 20% less absorption, it has the potential to affect seizure control and the patient may experience breakthrough seizures.

Respected neuropharmacologist and epileptologist Professor Frank Vajda explains this concern.

‘Antiepileptic drugs are a special case of drugs, which have a narrow therapeutic index. This means that the dose of the drug which is effective in preventing seizures is only a fraction above that which may not be effective or may produce unwanted effects.

‘It is therefore important that the drugs should be used in the same effective dose, a stable therapeutic dose, as they have been in the past, keeping the person with epilepsy seizure-free.

‘The problem is that generics are tested only superficially and, in the opinion of many, this process is inadequate.

‘The process involves a small number of volunteers – not patients with epilepsy – being given a single dose of the generic drug – not multiple doses, and not repeatedly – to compare plasma levels, but not effectiveness, on the basis of the 20 per cent rule. This implies that if the blood level over the short period of testing is above or below 20 per cent of the blood level achieved by the designer drug, the two types of drug are regarded as “bioequivalent”.

‘However no account is taken of the severity of illness, other drugs present and multiple other factors that affect blood levels. This testing criterion in any case is flawed, as we are treating patients, not blood levels.’

Branded vs generics?

The information presented here is not intended to question the efficacy of generic AEDs in their own right. It is not the prescribing of generic AEDs that appears to be the problem, it is switching between brands.

When AED therapy is initiated, the neurologist will prescribe the most appropriate drug to treat that particular type of epilepsy. This may be a branded AED or a generic AED, however once the person is stabilized on that formulation, it should not be switched.

Expert bodies including the Epilepsy Society of Australia, the American Academy of Neurologists, the National Institute of Clinical Excellence (UK) and the Scottish Intercollegiate Guidelines Network, all advise that a patient with well controlled epilepsy should not have the preparation of drug, whether generic or branded, substituted.

Is switching AEDs risky?

Switching between formulations of AEDs, whether it be branded to generic, generic to branded, or generic to generic, has the potential for devastating consequences for people with well controlled epilepsy.

Risks associated with switching AEDs include breakthrough seizures causing injury, loss of employment and/or driver’s license, an accident while driving, and a loss of faith in medication,

and psychological distress; toxicity and associated side effects; avoidable hospitalization, and increased doctor visits in order to regain seizure control.

In discussing this point, Professor Vajda acknowledges that ‘formal studies to show breakthrough seizures on changing to generics are scanty, as they are not a financial proposition for companies. However, anecdotal reports of seizures after a switch are numerous.’

Professor Vajda cautioned, ‘The treatment for a person with epilepsy ought not to be changed, changing from one preparation to another is a major alteration. This may also work the other way. If a patient is on a generic drug, changing him or her to the branded drug may be fraught with a similar risk of destabilization. Hence switching is ill advised and may be dangerous.’

In patients with poorly controlled epilepsy, it is reasonable for your neurologist to suggest that you switch AEDs, either to a generic or branded form. However, this will be done under medical supervision as there will be an appropriate crossover period for the drugs, when the dose of the old will decrease and the dose of the new will increase until the therapeutic dose is reached. This is quite different to switching formulations at the time the prescription is dispensed.

As with all medication switches, there is also the risk of the consumer becoming confused as the drugs differ in appearance, name, colour, shape and size, smell and taste.

With many generic formulations of a branded AED now available this is a real concern, an example being lamotrigine. Apart from the branded drug Lamictal™, there are nine different generic formulations that can be dispensed, raising other issues of concern. Professor Vajda elaborates,

‘Having several drugs representing the same components, may also cause confusion, especially in the frail and elderly, and those with a cognitive disability. It may lead to no-compliance and to storing different preparations of antiepileptic drugs in medicine cupboards and, after the urging of relatives and doctors to comply with instructions, this may lead to overdose or further confusion.’

What price do you put on seizure control?

Maintaining health, is a costly business. As consumers we are always looking to save money on that headache, hayfever or flu tablet and generic formulations often provide that saving.

Under the Pharmaceutical Benefits Scheme (PBS) the maximum cost for a pharmaceutical benefit item at a pharmacy is generally \$32.90 for general patients and \$5.30 for concession patients. The PBS minimum pricing policy states that only the cheapest products of a particular medicine are available for substitution. The difference between the cheapest product (generic) and the more expensive branded drug is known as the *brand premium*.

In the case of AEDS, if you choose the branded AED over the generic formulation, it will cost you an extra \$1 to \$3 per prescription. Currently in Australia this applies to four branded AEDs: Tegretol, Neurontin, Lamictal and Epilim.

So the next time you have your prescription dispensed at the pharmacy and the assistant asks you if you would like the cheaper brand, ask yourself the following questions,

‘Is saving a few dollars worth the risk of potentially having a breakthrough seizure and its possible consequences of accident or injury, loss of driving license, loss of work time or even loss of employment?’

‘What cost do I place on seizure control and peace of mind?’

For people with epilepsy, the potential costs of switching AEDs far outweigh the few dollars saved.

Epilepsy Australia urges people with epilepsy to:

- Know the brand name of the AED you were originally prescribed
- Pay close attention to every prescription dispensed and query if it is different from your usual prescription
- Refuse substitution if asked at the pharmacy
- Request your doctor to check the *Brand substitution not permitted* box at the time of prescribing