Monitoring of **generic medicines** and **brand changes**

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Reports to CARM following brand change

Unlike other national monitoring centres internationally, CARM receives reports of patients' adverse experiences on changing brands of medicines that contain the same active ingredient. Almost exclusively, these reports follow a change in brand subsidy by PHARMAC, but also occur when the availability of a medicine changes for other reasons.

The initial reports of adverse experiences are usually received by CARM within the first few weeks following the brand change. Typically, these reports describe a loss of therapeutic effect when compared to the original product. Other events are also described, the most frequent of which are gastrointestinal (nausea vomiting diarrhoea), skin (rash and/or pruritus) and neurological events (headache and or dizziness). Occasional reports are suggestive of increased therapeutic effect such as hypotension with enalapril.

CARM has received reports following brand change for a range of medicines since 1998. However, CARM began to focus on this phenomenon in 2001 when the frequency of reporting increased following the change to a generic version of fluoxetine.

Following a brand change, reports generally follow a predictable pattern that peaks typically in the range of 15-40 reports and then declines over a three month period (Figure 1).

In the fluoxetine graph in Figure 1, the first series represents the change from Prozac to Plinzine (innovator to generic), and the second period the change from Plinzine to Fluox (generic to generic).

This pattern with an initial peak then decline, despite the new medicine continuing to be available, suggests that the adverse reaction reports are a phenomenon of the change process rather than medicine *per se*.

Reports associated with brand change are assessed and evaluated at CARM in the same manner as all other reports of adverse events. This includes assigning the reaction terms and causal association and then addition to the to the CARM database. The receipt of each additional report contributes to the emerging pattern. The nature of the

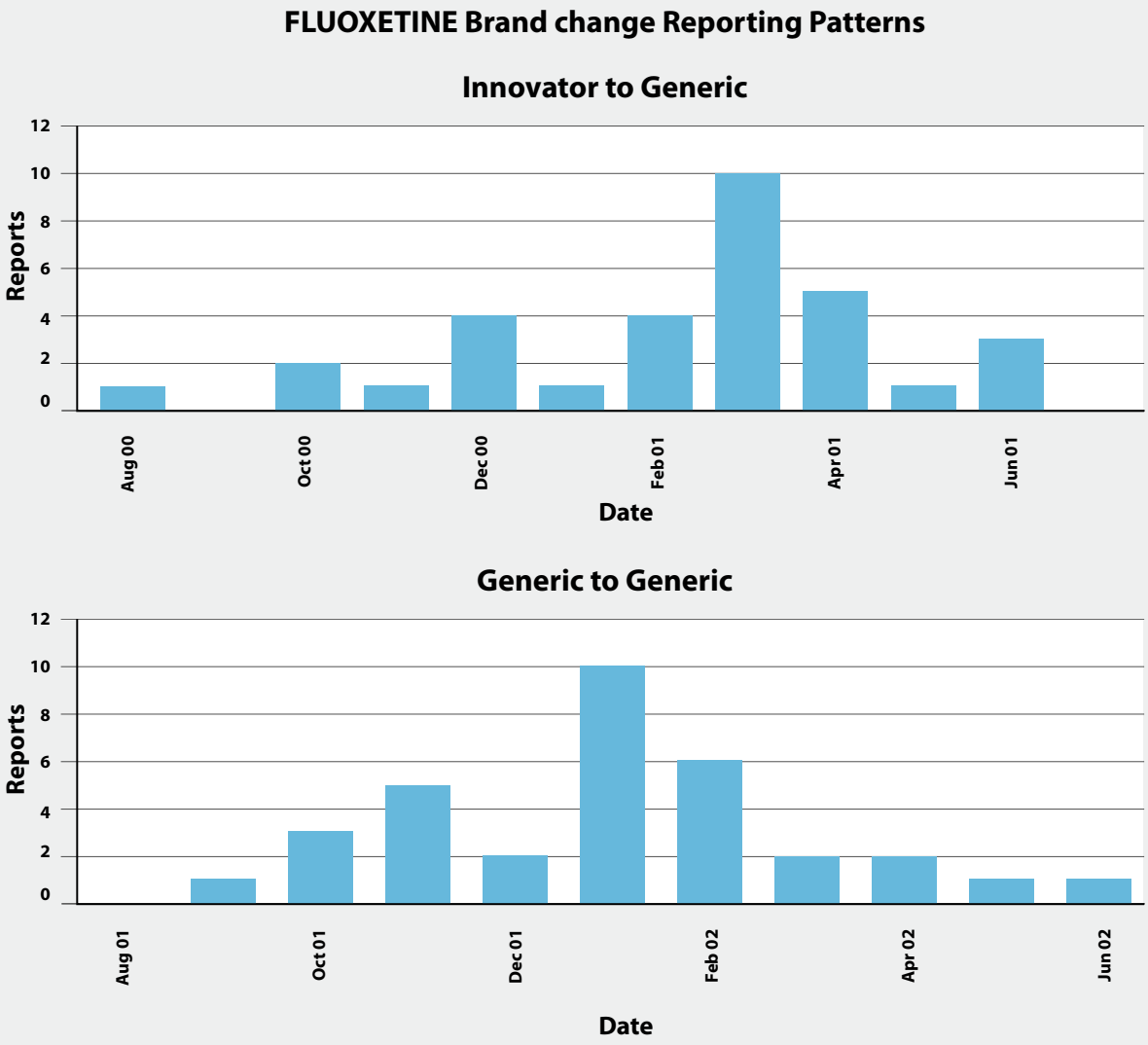

Figure 1: An example of early brand change reporting patterns for fluoxetine

events, their frequency and duration are monitored over time.

If the few isolated reports begin to increase to more frequent or regular reporting, Medsafe is notified of the existence of a potentially new brand change phenomenon and a brief overview of the spectrum of the reported events is provided with regular updates. Each quarter, the Medicine Adverse Reactions Committee (MARC) receives a summary report of new and ongoing brand change reports.

Although most brand change issues follow a predictable and transient pattern, deviations from this pattern provide a basis for identifying signals of a potentially more significant problem.

The existence of a potential issue is formally brought to the attention of Medsafe and MARC for further consideration when:

- there are more than 40 reports for any brand change
- the issue persists for more than three months without indication of decline
- the events themselves, irrespective of number of reports or duration, are of a serious nature

It has become apparent from the content of the reports that media attention, internet blog sites and anti-PHARMAC sentiment are important factors for some brand changes that result in high numbers or sustained reporting.

Some recent examples of deviations from the expected pattern observed by CARM that have resulted in further attention include the following:

Ritalin SR to Rubifen SR

The change from Ritalin SR to Rubifen SR in 2006-7 resulted in CARM receiving over 200 reports of reduced therapeutic effect as well as a more concerning presentation of aggressive and other psychiatric reactions largely in children, but also adults. There were suggestions that these behaviours could be part of the spectrum of ADHD manifestation, or that they reflected social resistance to the new product.

Action taken by Medsafe and MARC resulted in extensive re-evaluation of Rubifen SR which confirmed that the product met all bioequivalence specifications. Further product testing was unable to demonstrate any composition factor that could account for the observed events. However, given the number and nature of the events, PHARMAC introduced special authority access to Ritalin for those who had reported psychiatric events of concern.

Eltroxin formulation change

The reports with Eltroxin were associated with a formulation change instituted by the manufacturer and not due to a switch to a generic medicine due to a funding change. However, the example serves well to demonstrate the pharmacovigilance process.

Eltroxin underwent a formulation change, introduced by the innovator manufacturer in late 2007. The formulation change was supported by bioequivalence data and approved in 25 other countries. At the time no alternative products were registered in New Zealand.

At the time of this change around 40 reports were received, however the fact that they persisted over a 6-8 month period (culminating in a total of about 1400) resulted in a review and report to Medsafe and MARC. The reports described reduced therapeutic effect, headaches, eye pain, allergic events and symptoms affecting the central nervous system such as memory and cognition disturbances. More extensive reviews were performed during the sustained reporting and Medsafe initiated an independent investigation of the product.

No adequate explanation for the reports was established. In addition, these reports appeared unique to New Zealand, despite the identical product having been marketed in other countries. Due to the scale of problem and reports of improvement on changing to an alternative unregistered product, Medsafe facilitated the registration of alternatives which were also subsidised by PHARMAC.

Making a report to CARM

Reports can include adverse effects or changed therapeutic response and are made on the standard CARM reporting card, online or through the *bestpractice* Adverse Drug Reaction module on the toolbar of your practice management system.

Telephone: **03 479 7247**

Website: **www.otago.ac.nz/carm**