

Medicines Adverse Reactions Committee

Meeting date	13 September 2018	Agenda item	3.2.1
Title	Brand switches in New Zealand		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Previous MARC meetings	<p>Brand switches have been discussed previously at the following meetings:</p> <ul style="list-style-type: none"> – 111th Meeting – 11 September 2002 Multiple brand switches discussed – recommended monitoring as part of NZ pharmacovigilance strategy – 131st Meeting – 13 September 2007 Rubifen SR brand switch – aggressive and defiant behavioural reactions – 135th Meeting – 11 September 2008 Eltroxin formulation change adverse reactions – 138th Meeting – 11 June 2009 Signal detection and evaluation in New Zealand A report was prepared by NZPhvC which highlighted the trend with reporting during brand switch periods at the time (Annex 1) 		
Prescriber Update	Prescriber Update 30(1):1, February 2009. <i>Eltroxin Update</i>		
Schedule	Prescription medicine		
Advice sought	<p>The Committee is asked to advise on:</p> <p>Where Medsafe can create risk minimisation measures to enhance public safety, improve public trust in Pharmac, Medsafe and the wider government, and reduce the potential for harm from adverse drug reactions associated with brand switches.</p>		

Table of Contents

1.0	PURPOSE.....	3
2.0	BACKGROUND	3
2.1	Bioequivalence and generic medicines	3
2.1.1	Introduction.....	3
2.1.2	New Zealand Regulation (Annex 2)	3
2.1.3	Clinical outcomes of generics	6
2.2	The nocebo effect.....	8
2.3	Brand switches	8
2.3.1	Pharmac’s role	8
2.3.2	International differences.....	9
2.3.3	Patient access to non-funded medicines	9
2.3.4	Public perception.....	10
3.0	ADVERSE REACTION REPORTING TRENDS.....	10
3.1.1	Methylphenidate	11
3.1.2	Enalapril.....	12
3.1.3	Simvastatin	14
3.1.4	Fluoxetine	15
3.1.5	Omeprazole	16
3.1.6	Venlafaxine	18
4.0	REPORTER TRENDS	21
5.0	ELTROXIN FORMULATION SWITCH (33)	25
5.1.1	Gardner & Dew, 2011 (34)	26
5.1.2	Faasse, Cundy & Petrie 2009 (33).....	27
6.0	DISCUSSION AND CONCLUSIONS	28
7.0	ADVICE SOUGHT	30
8.0	ANNEXES.....	30
9.0	REFERENCES	30

1.0 PURPOSE

Over the past two decades, generic medicines have become an established part of the New Zealand healthcare system. Due to the operations of Pharmac, generally only one brand of a medicine is subsidised and readily available. The funded brands may change as a cheaper generic medicine becomes available, and patients must undergo a “brand switch”. Although the new brand is an approved generic that meets New Zealand bioequivalence standards, there have been instances where a number of patients have experienced adverse reactions when switching brand, culminating in reports to the Centre for Adverse Reactions Monitoring (CARM).

This paper reviews the trends in brand switches that attracted higher than expected reporting and seeks to identify how Medsafe can act to enhance public trust in the healthcare system, as well as ensure patient safety is assured when a brand switch occurs. Medsafe’s goal is to ensure that brand switches are smooth in transition and nation-wide problems, such as the current issue with Enlafax (venlafaxine), do not occur.

This paper has a focus on clinical effectiveness and safety outcomes of generic medicines within the scope of Medsafe’s function.

2.0 BACKGROUND

2.1 Bioequivalence and generic medicines

2.1.1 Introduction

Generic medicines are defined as medicines which have the same chemical substance as the originally developed and patented innovating drug, but may differ in characteristics such as manufacturing process, formulation, excipients, colour, taste and packaging (1). The provision of generic medicines is an important aspect of modern healthcare systems. They are widespread in use and economically favourable. Due to lower costs of production compared with innovator products (where extensive clinical trial research is required), generic medicines can lead to considerable healthcare savings. In 2012, 84% of prescriptions in the USA were filled with generic medicines. The use of generic medicines in the USA saved \$1.67 trillion between 2007 and 2016 (2).

Bioavailability is a measurement of the extent of a therapeutically active medicine that reaches the systemic circulation and therefore is available at the site of action. This is assessed using three pharmacokinetic variables:

- the area under the blood drug concentration versus time curve (AUC)
- the maximum blood concentration (C_{max})
- the time to reach maximum blood concentration (t_{max}) (3).

The World Health Organisation defines bioequivalence as “two pharmaceutical products that are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities in terms of rate (C_{max} and t_{max}) and extent of absorption (area under the curve (AUC)), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same”(4). When an innovator and generic medicines have no significant differences between these three parameters, they are considered to be bioequivalent and therefore the generic medicine is considered to be, clinically, the same as the innovator product (3).

2.1.2 New Zealand Regulation (Annex 2)

A generic product can only be approved in New Zealand if the sponsors can prove bioequivalence to a product that is already approved, or another appropriate reference medicine. This provides bridging of the full clinical dataset held by Medsafe for the innovator medicine to support efficacy and safety of the generic medicine entering the New Zealand market.

Medsafe only accepts bioequivalence studies that are conducted in accordance with the International Conference on Harmonisation (ICH) *Guidance on Good Clinical Practice*, and the principles of Good Manufacturing Practice and Good Laboratory Practice should be adhered to where applicable.

There are four acceptable options for a reference product:

- using the innovator medicine obtained from the New Zealand market,
- using an innovator medicine obtained from an overseas market, where *in vitro* tests show this to be same as the innovator product approved in New Zealand (essential similarity testing),
- using an innovator medicine obtained from the Australian market, where essential similarity may be assumed if sufficient evidence is provided,
- if no other option is possible, using an alternative reference product sourced from the New Zealand market.

New Zealand follows the European Medicines Agency *Guideline for Investigations of Bioequivalence* (Annex 3) and *Guideline on the pharmacokinetic and clinical evaluation of modified-release dosage forms* (Annex 4) for establishing bioequivalence for oral medicines.

2.1.2.1 Bioequivalence study design

If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally, at least five elimination half-lives are necessary to achieve this. Other study designs such as a single dose study or parallel designs may be accepted if the above is not possible or appropriate.

The number of subjects to be included in the study should be based on an appropriate sample size calculation. The number of evaluable subjects in bioequivalence studies should not be less than 12. In order to reduce variability not related to differences between products, the studies should be performed in healthy volunteers unless the drug carries safety concerns that make this unethical. Subjects should be at least 18 years of age, and have a Body Mass Index between 18.5 and 30 kg/m².

2.1.2.2 Establishing bioequivalence

In studies to determine bioequivalence after a single dose, the parameters to be analysed are generally $AUC_{(0-t)}$, and C_{max} (Figure 1). For these parameters, the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of 80-125% (Figure 2). If rapid release is claimed to be clinically relevant and important for onset of action, or is related to adverse events, there should be no apparent difference in the median t_{max} and its variability between test and reference product.

Figure 1: Simulation of drug concentration versus time for two drug products (3)

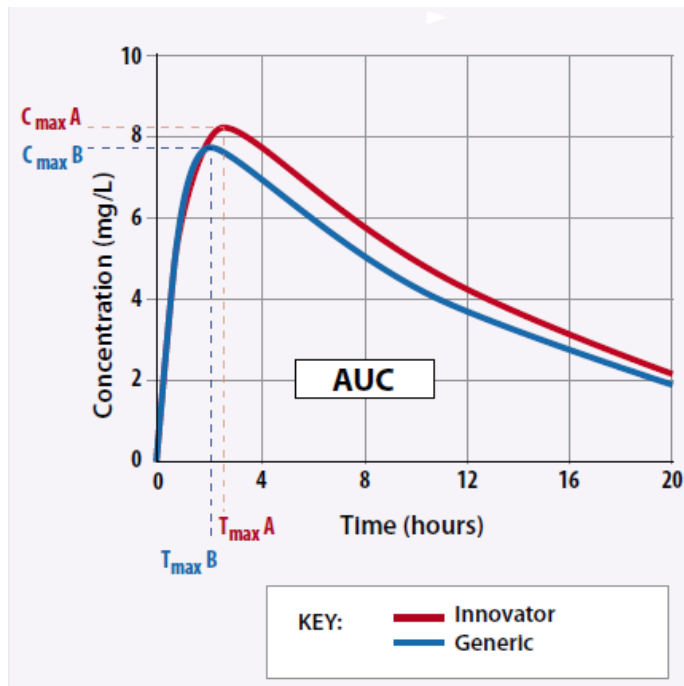
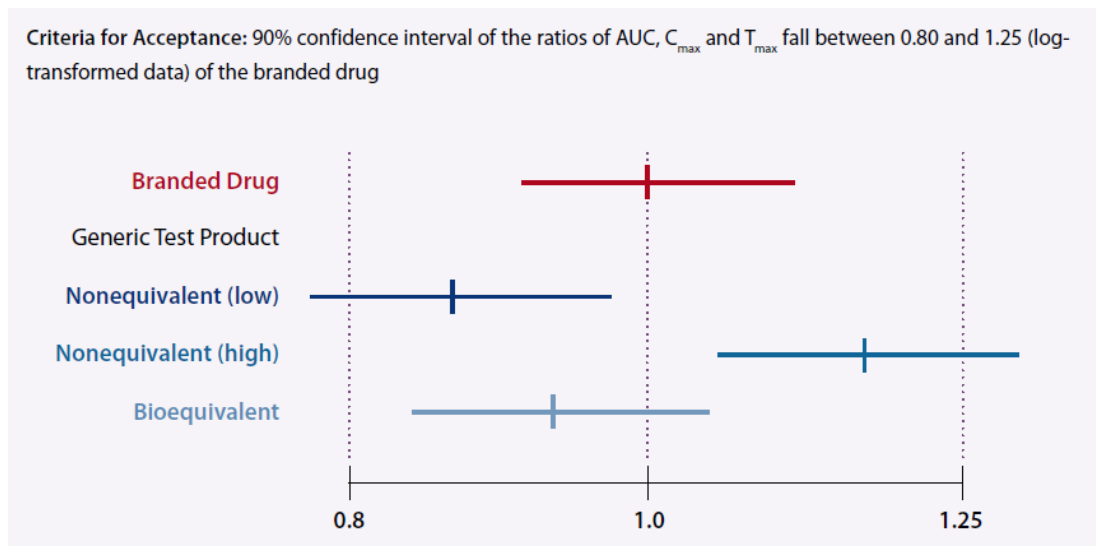


Figure 2: Bioequivalence confidence intervals (3)



2.1.2.3 Narrow therapeutic index products

A medicine with a narrow therapeutic index (NTI) has a very small margin between therapeutic and toxic plasma levels. As such, small differences in the bioavailability of an NTI medicine can have significant consequences. In this case, the 90% confidence interval for the ratio of the test and reference products should be contained within a narrower acceptance interval of 90-111%. Where C_{max} is of particular importance for safety, efficacy or drug level monitoring, this acceptance interval is also applied.

If two pharmaceutically equivalent medicines of the same active ingredient, dose form, indication and dosage have been shown to be bioequivalent by the above standards, they are considered interchangeable. This, however, does not apply to medicines where its inherent nature or pharmacokinetic properties of the active ingredient render it not appropriate to interchange. If this is the case, warnings are required on the New Zealand data sheet, as well as information about switching formulations (if appropriate).

Once a generic medicine has gained approval in New Zealand, it is subject to the same regulations as all other medicines.

2.1.3 Clinical outcomes of generics

Although wide-spread regulatory acceptance that generic medicines are clinically acceptable and economically superior to innovator medicines, there remains scepticism in the public about their safety and effectiveness. As generic medicines are not subject to the more rigorous approval process of innovators, there is some people express concerns about clinical outcomes. This scepticism comes from consumers, academics and health professionals alike and presents difficulties for regulatory agencies. These beliefs are further supported by pharmaceutical companies who, at times, have lobbied against the use of generic medicines in order to protect their product (5, 6). The core issue is that clinical outcomes are not evaluated for generics, rather they are assumed based on chemical and pharmacokinetic equivalence.

2.1.3.1 Effectiveness

A number of academic studies have been done to test the equivalence of generics to innovator products. Cardiovascular generic medicines have been investigated for clinical efficacy and safety end points. This provides investigators with a group which makes up the largest portion of outpatient prescription drug spending. In 2008, Kesselheim et al (7) completed a systematic review and meta-analysis of the clinical equivalence of generic and brand-name drugs used in cardiovascular disease. The study reviewed 47 randomized controlled trials (RCTs) and observational studies, between 1984 and 2008, where there was a comparative evaluation of one brand-name drug and at least one generic version produced by a distinct manufacturer. The meta-analysis suggested no evidence of superiority of brand-name to generic drugs in measured clinical outcomes among these studies. The studies were limited in that they investigated small, healthy populations, were primarily bioequivalence studies that also tested clinical outcomes, did not have sufficient power to test clinical outcomes, and were evaluated by testing for superiority rather than non-inferiority.

Additional population-based studies investigating statins (8) and anti-hypertensives (9) have also shown that innovator medicines are not superior to generics in real world clinical practice for maintaining therapy and preventing CV outcomes. The studies largely accounted for the limitations in many of the previous studies. The cumulative outcome of these studies is that where medicines regulators have approved a generic medicine on the basis of international bioequivalence standards, it can be expected to have no significant differences in clinical outcomes in comparison to the innovator.

In 2018, Desai et al (10) published a large cohort study where a number of medicines were investigated. Patients who switched from an innovator to a generic medicine were followed for switchbacks to the innovator in the year after starting the generic. This study had significant power, following over 200,000 brand switches. The average switchback rate was 8.2 per 100 person years across all drug products. The reasons for switching back to the previously used brand were not investigated. Although not an investigation of direct clinical end points, it does provide an indication as to patients' general tolerability of generic medicines.

Comments

These studies provide evidence that Medsafe's current regulatory scheme is sufficient in ensuring the safety and clinical efficacy of generic medicines. It is unlikely that gaps in regulation are the reason for the higher than expected reporting of ADRs.

2.1.3.2 Ineffectiveness

Psychotropic medicines have been another focal point for studies comparing generics to brand-name medicines. A literature review by Desmarais, Beauclair and Margolese (11) on generic psychotropic medicines encouraged brand-switching decisions to be done on an individual basis with close

monitoring throughout the transition. Notably, harmful effects of switching patients with epileptic disorders from original to generic anticonvulsants were described, especially with valproate, phenytoin, carbamazepine and primidone. In many cases, a switchback was required due to inadequate seizure control or toxic effects of the medicine. In 2014, the MHRA published a drug safety update advising on brand switches for anticonvulsants (12). This followed the Commission on Human Medicines (CHM)'s review of spontaneous reports and literature. The advice included a categorisation of anticonvulsants into three groups:

- 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 reasons such as patient anxiety and risk of confusion or dosing errors

This was a risk minimisation measure, as the loss of seizure control and/or worsening of side effects could be explained by chance associations, but the causal role of switching could not be ruled out in most cases. The review did not conclude that the brand switch were the cause of adverse effects, however the measures undertaken were expected to reduce the incidence of them.

Anticonvulsants have also been shown to have higher rates of switchbacks when compared to cardiovascular medicines and SSRIs (13). The high rate of switchbacks is a concern as it potentially indicates a higher rate of adverse events associated with the generic. This further supports the risk minimisation measures undertaken by European countries and gives evidence that this is an issue specific to anticonvulsants and cannot necessarily be extrapolated to all generic medicines.

Desmarais et al (11) also reviewed antidepressants, antipsychotics and anxiolytics. However, for these medicines, primarily case reports were published. Where controlled studies were done, no statistically significant results were produced. Some studies in this review reported that bioequivalence was not met when pharmacokinetic parameters were re-tested by independent researchers. This may indicate that these medicines may be subject to some inter-patient variation in bioavailability, assuming the study was appropriately designed and carried out. However, bioequivalence studies with the power required for regulatory approval would be expected to overcome any inter-patient variation.

Comments

Overall, the evidence favours the effectiveness of generic medicines. Evidence for ineffectiveness of generic medicines appears to be primarily from case reports and replicated bioequivalence studies. Evidence from controlled studies is limited in comparison to studies showing the effectiveness of generic medicines. The exception to this appears to be with anticonvulsants, where the dose/medicine to seizure control relationship can be specific to an individual patient and a brand-switch would not be appropriate.

In New Zealand, the Pharmacology and Therapeutics Advisory Committee (PTAC) advise Pharmac on clinical considerations for funding. This would include cases where brand switches would not be appropriate, such as with certain antiepileptic medicines.

2.2 The nocebo effect

The term nocebo comes from the Latin “to harm”. The term describes the opposite of the placebo effect, where positive outcomes occur based on psychological beliefs of benefit, rather than a pharmacological intervention. Therefore, the nocebo effect is where negative outcomes occur based on psychological beliefs of harm. The nocebo effect may be causative of some adverse drug reactions in the same way the placebo effect can create clinical benefit. It is an expectation about the negative treatment outcomes. If a patient expects a side effect, the side effect is more likely to occur (14).

The phenomenon helps to explain how some seemingly unexplainable outcomes occur. Although never proven to cause adverse effects, reactions such as headaches and dizziness from “heavy WiFi signals” in CBD areas or wind turbines are likely due to the nocebo effect. People believe there are issues with something, and their body develops a reaction in response (14). Reactions due to the nocebo effect are not merely beliefs that something has occurred, the reactions are often clinically diagnosable and have a real effect on the patient.

One way in which the nocebo effect can cause adverse drug reactions is through so called “media storms”, where published studies and information are widely disseminated by the media. In some cases, this could be viewed as “scare-mongering” by the media. An example of where this has occurred was when the British Medical Journal (BMJ) published an article, in 2013, suggesting the side effects of taking cholesterol-lowering statins may outweigh the benefits for some (15). The media highlighted adverse effects such as muscle pain with statins. As a result, an estimated 200,000 patients stopped taking the drug within six months of the story being published, many due to experiencing adverse reactions. There was also an increase in the number of reports of rhabdomyolysis over this time. The incident has since been believed to be due to the nocebo effect (14).

There lies a question of whether the nocebo effect may be the cause of adverse effects patients suffer with generic and biosimilar medicines due to the pre-existing scepticism of them in the general public. A 2015 Finnish report showed that around a quarter of patients discontinued taking an infliximab biosimilar due to perceived loss of efficacy or increased side effects (16). Other studies have shown that perception of cost can enhance the nocebo effect (17). It has also been postulated that certain cultures, or groups of people, are more prone to having beliefs that shape nocebo and placebo responses (14). There is a noticeable indication that the nocebo effect does indeed cause adverse reactions in some patients who take generic medicines.

The nocebo response creates an ethical dilemma for clinicians and regulators alike. Patients have the right to be fully informed which includes all relevant information on any medicine they have been prescribed. However, from a psychology perspective, this may be seen as counter-productive due to the nocebo effect. Ultimately, it would be unethical to withhold information from patients; therefore, the framing of all information given to patients is vital when considering potential negative outcomes from medicines.

2.3 Brand switches

2.3.1 Pharmac’s role

Pharmac is the New Zealand government agency which makes pharmaceutical funding decisions for New Zealand. Established in 1993, they make choices about District Health Boards’ spending on vaccines, community and cancer medicines. Pharmac also makes decisions about the medicines funded in DHB hospitals and is working towards a budget management of hospital medicines and medical devices (18).

For most medicines, the unique management of the pharmaceutical budget in New Zealand by Pharmac results in a single brand being funded through a contract over a certain amount of time, so called sole supply. Funded brands are listed in the Pharmac Pharmaceutical Schedule. It should be

noted that there is currently a separate hospital medicines list, which operates differently to that of the community schedule. In most cases, an innovator medicine is initially listed in the schedule when the medicine first enters the market. After the patent of the innovator expires, generic medicines enter the market after approval by Medsafe (see section 2.1.2 for regulation of generic medicines). As these medicines are frequently more economically favourable than their innovator counterparts, Pharmac explore avenues to fund a generic. In most situations, unless the innovator dramatically lower its price, the innovator company will lose funding for the medicine and the generic will have sole supply. Generic medicines may also be produced by the innovator manufacturer; these are considered to be authorised generics (10). Generic to generic brand switches can also occur. In some situations, multiple brands may have funding. These switches usually have a crossover period to allow for patient/health professional adjustment.

This switch in funding by Pharmac is, for the purpose of this paper, defined as a brand switch. Patients have no choice but to take the funded brand of the medicine. Although it may be possible for pharmacies to supply patients with non-funded brands, the patients will be paying full market price for their medicine and supply is not guaranteed from the company (on the contrary, the pharmaceutical industry has a supply obligation as part of their contract with Pharmac in order to have their medicines subsidised). The public's perception of Pharmac varies. Many people see the benefits Pharmac provides New Zealanders by ensuring very low prices for their medicines (currently \$5 per prescription item) and that saving on generics may make it possible to fund new treatments. Others may see Pharmac as dictating which medicines, and brands, people can and cannot take. From the perspective of brand switches, people have referred to Pharmac as "being cheap" and funding "ineffective knock offs from India" (6). The lack of trust in Pharmac, combined with scepticism about generics, has resulted in widespread media attention, higher than expected numbers of ADR reports and general public discontent over some brand switches.

2.3.2 International differences

New Zealand is in a unique situation with a tightly managed pharmaceutical budget. Overseas pharmaceutical budgets may be larger, their markets operate with more independence from the government, and/or multiple brands are readily available to the market. With little comparisons to how pharmaceutical budgets are managed overseas, it is difficult to look to other countries for guidance on how to manage our budget in a fiscally responsible manner. The issues with brand switches do not tend to be as prevalent overseas where if a brand is less tolerated, there is the option to change to a different brand. This is often not an option for New Zealanders, which can spread discontent, enhance the nocebo effect and lead to public health problems.

An example of how another nation manages brand availability for patients is Sweden. Each month, they have a tender to declare the "medicine of the month (PV)" for every medicine group. There are two other brands per group who also receive funding during that specific month but can only be used if there is a problem with the PV. This is usually determined by the lowest price. As a prescriber, you can refuse to prescribe the PV for a patient for medical reasons, and any brand available is funded. As a patient, you can refuse the PV but then you have to pay market price for another brand. Complaints in Sweden are usually due to confusion between the different brands, and the risk of medical errors. However, due to other brands being available if required, adverse reaction patterns, like those seen in New Zealand, do not appear to occur.

2.3.3 Patient access to non-funded medicines

Although the vast majority of patients can only access the funded brand at the subsidised price, Pharmac does provide options for patients with exceptional circumstances. Their Exceptional Circumstances Framework generally considers funding decisions in exceptional circumstances that fall outside of the Pharmaceutical Schedule funding process. For accessing non-funding brands, the Named Patient Pharmaceutical Assessment (NPPA) is required.

The NPPA policy sets out three core principles which must be met for an application to be considered for funding. The NPPA policy:

1. provides a pathway to consider those whose clinical circumstances cannot be met through the Pharmaceutical Schedule at a given point in time
2. complements the Pharmaceutical schedule and the Schedule decision-making process
3. is designed for individual assessment

The application is then assessed against the Factors for Consideration – the framework under which all medicine funding applications are assessed under. However, Pharmac does not consider any information obtained from treatment not funded by Pharmac, non-clinical circumstances and patient preference.

Comments

These three factors make it difficult to obtain a NPPA for a brand of medicine that is not funded. It is unlikely that patients would be able to switch back to a non-funded brand unless there was definitive clinical evidence of need.

2.3.4 Public perception

In 2016, a survey was conducted by researchers at the University of Auckland to better understand New Zealand-patients' views on brand substitutions, their opinions on co-payment options and general understanding of the topic. Of the 194 patients surveyed, most respondents indicated preference towards the currently subsidised brands with little desire for alternatives. Half were willing to contribute towards paying for their own choice in brand, however the maximum contribution nominated was disproportionately lower than the real cost of the medicine. The survey suggested that although most patients had experienced brand switches without problems, a lack of knowledge about substitution does persist. The study was, however, limited in that only three medicine classes (lamotrigine, statins and calcium channel blockers) were investigated. The authors suggested that there may be additional gain in ensuring New Zealanders are aware of the full cost of their medicines. This would help reinforce the benefits of the Pharmac model and increase public trust (19).

3.0 ADVERSE REACTION REPORTING TRENDS

Annex 1, section 4.3.2, discusses the trends with brand switches in New Zealand up until 2009. The evaluation stated:

CARM has received reports of brand-switch reactions for a diversity of products since 1998. However, CARM began to focus on this phenomenon in 2001 when the frequency of reporting dramatically increased following reports associated with the use of a generic fluoxetine product. Generally brand-switch reports follow a predictable pattern that peak typically in the range of 15-40 reports) and decline over an approximately 3 month period. The reasons for this have not been investigated but suggestions include patients having either re-titrated their dose to achieve therapeutic effect, chosen to bear the cost differential in favour of the original product they were on or that these effects diminish with continued use.

Brand-switch reports are assessed and evaluated at CARM in the same manner as all other reports of adverse events – i.e. the events are assessed to assign reaction terms and causal association, and are then added to the CARM database. The receipt of each additional report adds weight to the emerging pattern. Once a new brand-switch issue is identified, it is carefully monitored with respect to the nature of events reported, the frequency and the number of incoming reports (and/or the duration over which the reports are received).

At the earliest stage when the first few isolated reports begin to increase to more frequent or regular reporting, Medsafe is notified of the existence of a potentially new brand-switch

phenomenon. A brief overview of the spectrum of the reported events is provided to Medsafe and then updated on a regular basis. Each quarter, the MARC receives a summary report of new and ongoing brand-switch reports.

Although most brand switch issues follow a predictable transient pattern, deviations from this pattern provide a basis for identifying those brand-switch reactions that may signal a more significant problem. A brand switch issue will be formally brought to the attention of Medsafe and MARC when:

- *there are more than 40 reports or*
- *the issue persists for more than 3 months without indication of decline, or*
- *where 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-switches which result in high numbers or sustained reporting.

The following sections review some of these brand switches, including ones that have occurred in more recent times. The general trends appear to be the same, albeit with varying magnitudes.

3.1.1 Methylphenidate

In September 2006, Pharmac announced they were switching the brand of their long acting formulation for methylphenidate. Methylphenidate is a medicine primarily used by children with the behavioural condition Attention Deficit Hyperactivity Disorder (ADHD). Ritalin SR was the original brand of methylphenidate used, however Pharmac announced that a new brand, Rubifen SR, would be subsidised. Pharmac provided a long transition time (November – April), where both medicines had funding, in order for doctors and patients to become well informed about the change. The change was forecast to save around \$3million over three years. Around 10,400 patients were expected to be affected by the change (20).

During the transition, CARM started receiving a number of reports of adverse reactions including a reduction in therapeutic effect with Rubifen SR. There was heightened media attention around this brand switch as well as discussions in forums for parents with children with ADHD (21). Medsafe re-evaluated the bioequivalence studies with additional expert advice and could not find any issue with the Rubifen SR formulation, despite the reports.

Medsafe referred the issue to the 131st Medicines Adverse Reactions Committee meeting on 13 September 2007. The recommendations from the MARC included requesting that Pharmac re-subsidise Ritalin until further investigation is done and that Medsafe undertake a Section 36 review of Rubifen SR (22). The Section 36 review did not reveal any new information and the risk benefit remained positive. Both Rubifen SR and Ritalin SR (reintroduced in September 2007) are still funded.

Comment

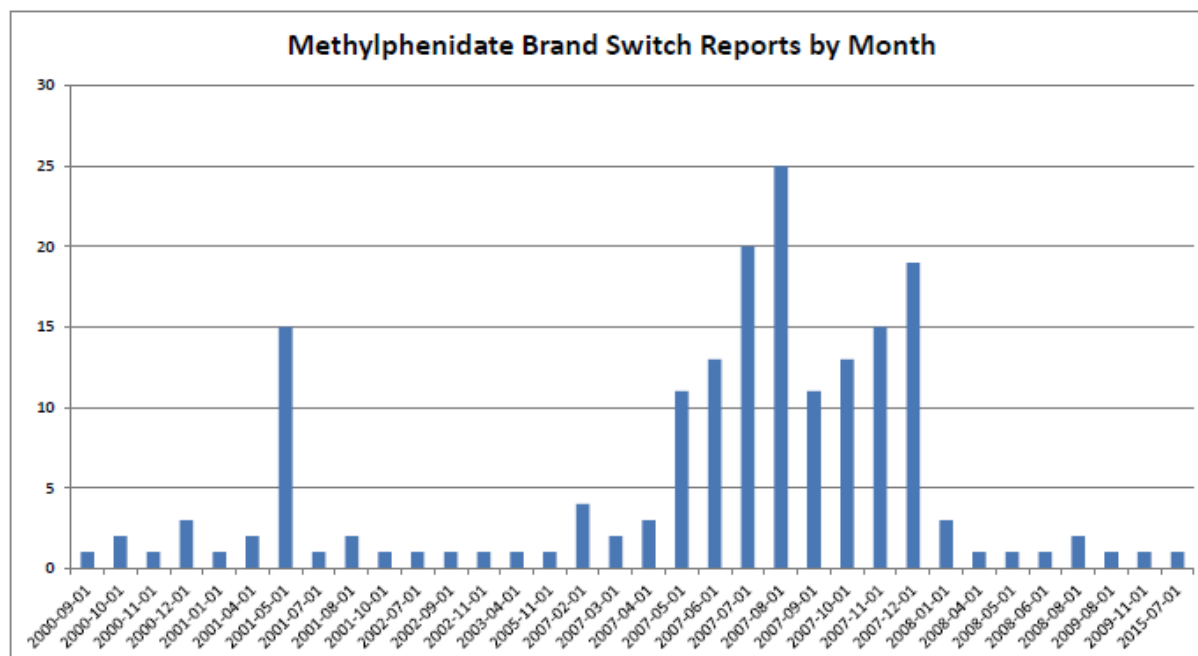
This brand switch is unique in that it the drug is used almost entirely by children. Therefore differing factors leading to ADRs must be considered to understand the cause of the reactions. The nocebo effect is less likely to be a factor as the children themselves likely have very little understanding of the medicine.

When considering future brand switches that may affect children, different risk minimisation methods may be required.

3.1.1.1 Reporting trends

A total of 181 reports have been received by CARM of an ADR associated with a brand switch. Figure 3 shows that from May 2007, there was a large increase in the number of reports received by CARM that indicated an adverse reaction occurring following the change in brand from Ritalin SR to Rubifen SR. A peak occurred in September, 5 months following the brand switch. A secondary peak can be observed in December, before tapering off completely in the months following. It is assumed the reports tapered off due to the reinstatement of funding for Ritalin SR, however there is no data on how many patients switched back to Ritalin SR and how many remained on Rubifen SR.

Figure 3: Number of reports of methylphenidate coded with “brand switch” received by CARM per month (n=181)



The most commonly reported terms were in the System Organ Class (SOC) of Psychiatric Disorders (n=44, 24% of total reports), primarily of *aggressive reaction* (n=28) and *concentration impaired* (n=5). 103 reports indicated that either the therapeutic response was decreased or the medicine was ineffective (57%). A mean of 1.83 (median=1) terms were reported each time.

Table 1 indicates the age and sex distribution of the reports. The most commonly reported group was children and adolescent males, although some reports are also of adult patients.

Table 1: Age and sex distribution of reports received by CARM of methylphenidate coded with brand switch (n=181)

	Male	Female	Unknown	Total
Unknown	5			5
02-05y	2	1		3
06-11y	67	11	1	79
12-16y	35	4		39
17-29y	21	2		23
30-39y	10	6		16
40-49y	2	8		10
50-59y	2	2		4
60-69y	2	0		2

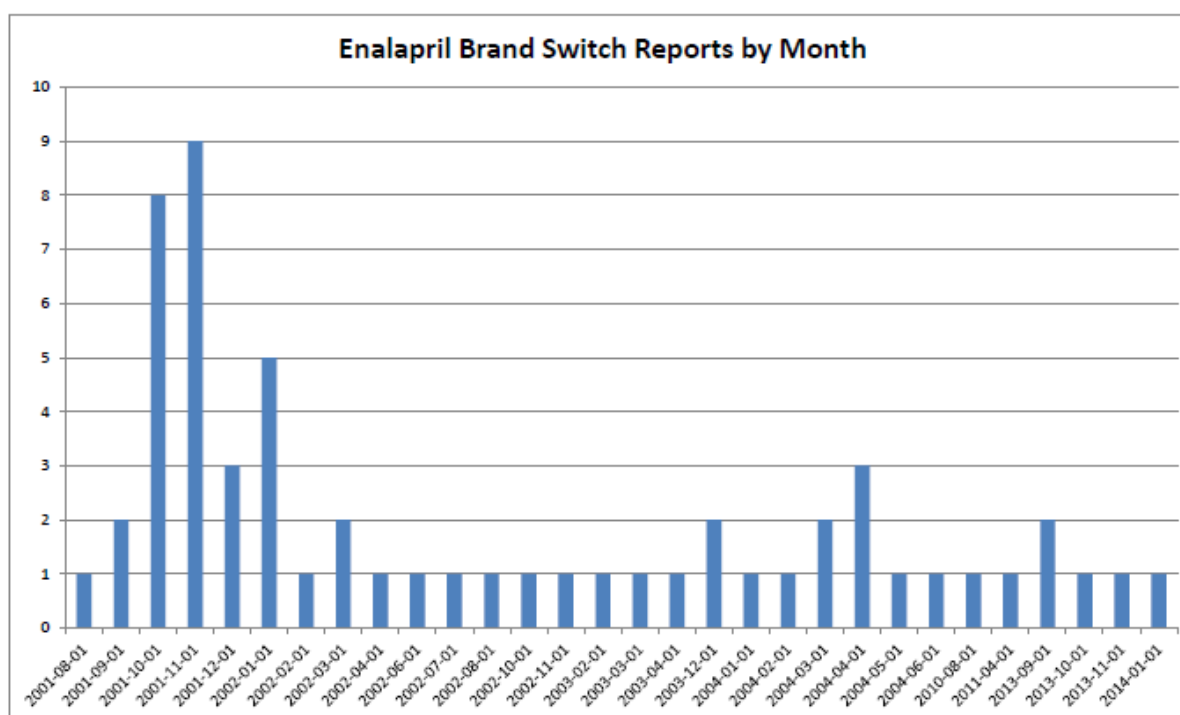
3.1.2 Enalapril

Enalapril is an ACE inhibitor used to treat hypertension and various cardiovascular diseases. Enalapril was first approved in New Zealand in 1984 under the brand name Renitec. In July 2001, Enahexal was

listed as the solely funded brand with the funding for Renitec ceased. Due to “quality” issues with Enahexal, the subsidy for this medicine was dropped in December 2002. This brand switch was also discussed at the 111th MARC meeting on 11 September 2002 on the topic of Brand-switch Related Reports. The Committee recommended at the time that monitoring of brand-switch patterns and problems should continue as part of the pharmacovigilance strategies in New Zealand (23). The most recent switch was in 2015, when Ethics enalapril became the sole funded brand in New Zealand.

3.1.2.1 Reporting trends

Figure 4: Number of reports of enalapril coded with “brand switch” received by CARM per month (n=58)



A total of 58 reports have been received by CARM indicating an ADR associated with a brand switch. Figure 4 shows major peaks are observed in 2001, indicating the brand switch from Renitec to Enahexal during this period. After early 2002 and the delisting of Enahexal, these reports tapered off and only isolated cases were reported. No further peaks were seen, despite other brand changes to enalapril, as recently as 2015.

Reported terms were of general symptoms, including dizziness (n=6), headache (n=7), nausea (n=5) and coughing (n=4). Fourteen reports (24.1%) indicated that the therapeutic response had decreased. Unlike other brand switches discussed in this paper, reactions related to the pharmacological profile or indication of the medicine were not reported. A mean of 1.93 (median=2) terms were reported each time.

Table 2: Age and sex distribution of reports received by CARM of enalapril coded with brand switch (n=58)

	Male	Female	Total
Not known	1	1	2
40-49		3	3
50-59	4	13	17
60-69	5	10	15
70-79	2	12	14
80+		7	7

Table 2 indicates that reports were primarily of females aged 50 and older. ACE inhibitors are primarily used by patients who suffer from hypertension or cardiovascular disease, which primarily affects older populations. The age range of reports correlates with expected usage.

Comments

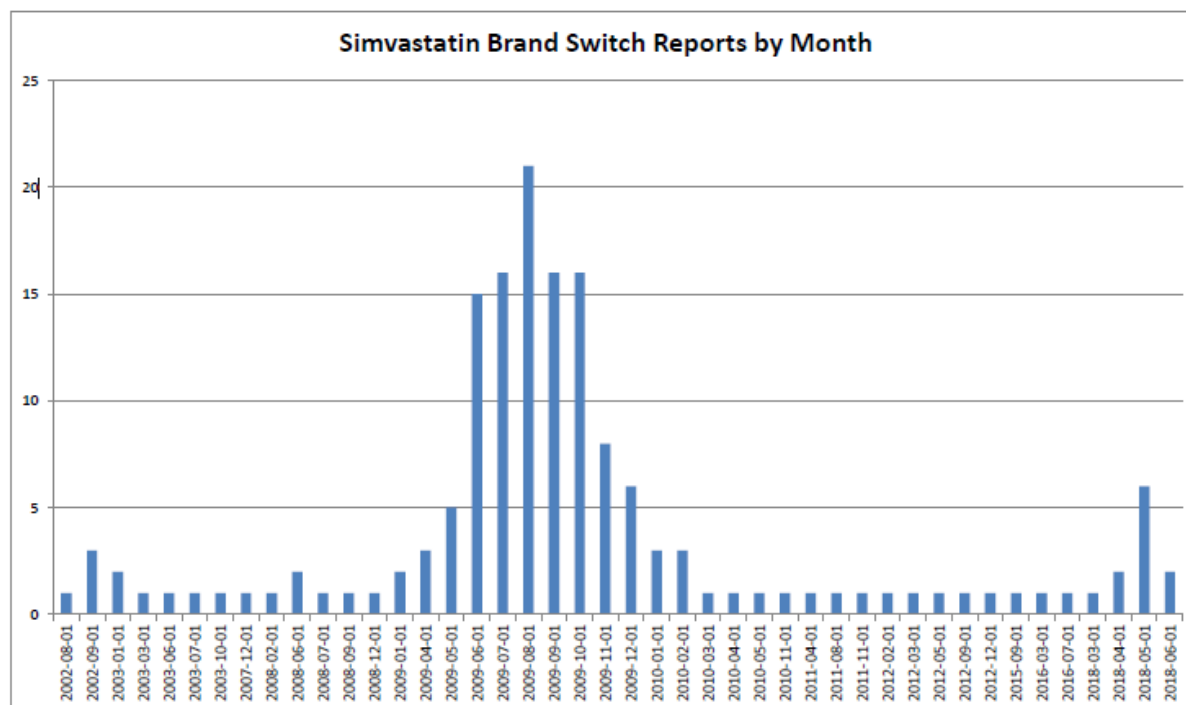
Enalapril follows a more “expected” trend, where general symptoms are reported and a small proportion of patients are affected. Multiple literature sources cited in this paper have stated this happens to a small proportion of patients who change brand of medicine.

3.1.3 Simvastatin

Simvastatin is part of a widely utilised class of medicines, statins, which are used to treat high cholesterol and reduce risk of cardiovascular disease. Statins are one of the most highly prescribed medicine in New Zealand. The innovator brand of simvastatin, Lipex, first gained consent in New Zealand in 1988. Although other generics were available beforehand, Pharmac began funding Arrow-Simva in 2009, ceasing their funding for Lipex. Pharmac published a brand change notification for this, informing the public about the change and what to expect. Due to the high usage and long period of funding, brand loyalty to Lipex was likely to be high.

3.1.3.1 Reporting trends

Figure 5: Number of reports of simvastatin coded with “brand switch” received by CARM per month (n=157)



There have been 157 reports received by CARM indicating an ADR associated with a brand switch of simvastatin. Figure 5 shows a clearly observable peak in 2009, around the time when Lipex lost its funding and patients switched to Arrow-Simva. The reports quickly tapered off and were not sustained for any period of time. Additional brand switches have occurred since, but have not cause any notable reporting rates.

Reported terms were of the SOCs musculoskeletal (n=19, 12.1%), central and peripheral nervous systems (n=17, 10.8%) and gastrointestinal symptoms (n=17, 10.8%). Reaction terms were general, with cramps (n=4), headache (n=5), dizziness (n=4), and diarrhoea (n=5). However, myalgia (n=11) and arthralgia (n=2), were also reported. These two reactions are known dose-related side effects of

statins (24). “Therapeutic response decreased” was not as commonly reported as with other brand switches (n=4, 2.5%). The mean number of reported terms was 1.91 (median=2) each time.

Table 3: Age and sex distribution of reports received by CARM of simvastatin coded with brand switch (n=157)

	Male	Female	Unknown	Total
Unknown	2	2		4
40-49y	4	4		8
50-59y	17	15		32
60-69y	21	37		58
70-79y	17	23		40
80y+	5	10		15

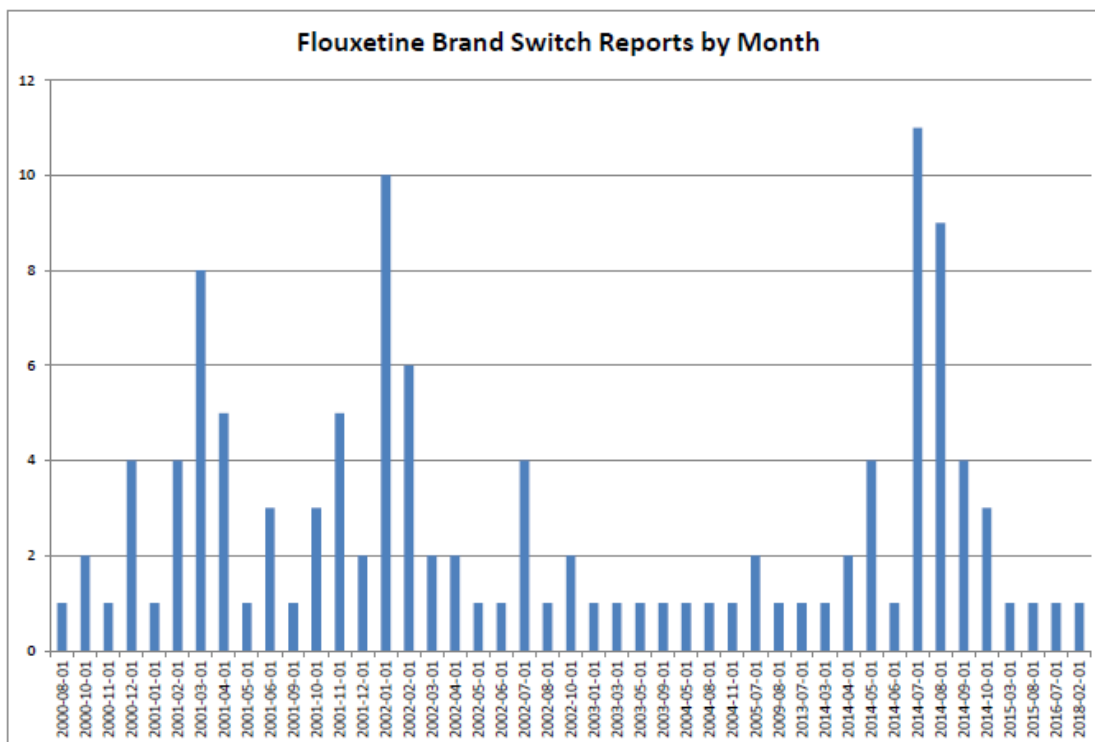
Table 3 shows that the age of affected patients is primarily 50+, as expected by the patient population who requires this medicine. The female to male is roughly equivalent, with slightly higher reporting rates in females.

3.1.4 Fluoxetine

Fluoxetine is an antidepressant medicine, of the selective serotonin reuptake inhibitor (SSRI) class. The innovator brand, Prozac, was first given consent in New Zealand in 1988. Due to the nature of antidepressants, Pharmac has not changed the brand many times for this medicine. Brand loyalty to Prozac was high, being one of the most commonly prescribed antidepressants (25). Initially, Pharmac changed the funding from Prozac to Plinzene. Soon after, Fluox received sole supply in New Zealand. Another switch occurred from the Fluox to Arrow-Fluoxetine, in 2013/2014. Arrow-Fluoxetine has remained that funded brand since. Fluox had previously been funded for the past ten years, allowing brand loyalty to develop for many patients (26).

3.1.4.1 Reporting trends

Figure 6: Number of reports of fluoxetine coded with “brand switch” received by CARM per month (n=120)



CARM has received a total of 120 reports indicating an ADR associated with a brand switch of fluoxetine. Although the magnitude of the peaks were lower, reporting trends in figure 6 indicate adverse reactions associated with the three different brand switches. Reporting rates remained low outside of these peaks.

Reported terms were primarily of the SOCs Central and Peripheral Nervous System (n=10, 8.3%), Psychiatric (n=9, 7.5%) and Gastro-intestinal (n=10, 8.3%). Reaction terms were highly varied, including anxiety, agitation, depression, aggressive reaction, tremor, headache, dizziness, nausea and dyspepsia. 40% of reports indicated that the therapeutic response was decreased or the medicine was ineffective (n=48). The mean number of reported terms was 1.79 (median=1) each time.

Table 4: Age and sex distribution of reports received by CARM of fluoxetine coded with brand switch (n=120)

	Male	Female	Unknown	Total
Unknown	1	0	1	2
12-16y	0	6		6
17-29y	3	4		7
30-39y	9	20		29
40-49y	5	20		25
50-59y	8	23		31
60-69y	3	11		14
70-79y	3	3		6
80y+	0	0		0

Table 4 shows reports were significantly higher in the female population, ages 30-69. Reporting rates for males were lower in comparison to other switches discussed in this paper.

Comments

Although lower in absolute numbers, the three reporting peaks associated with fluoxetine provide a good parallel for the current problems with venlafaxine as the medicines have the same indications. The trends indicate that we can expect reports to ease off as patients adjust to their new medicine or find an alternative.

3.1.5 Omeprazole

Omeprazole was first approved in New Zealand in April 1990. It is approved to treat reflux oesophagitis/reflux disease, acid-related dyspepsia, peptic ulcers, and a number of other gastrointestinal-related conditions. Omeprazole has become one of the most commonly used medicines in New Zealand with 495,000 people receiving a prescription for this medicine at some point during 2016 (as per DataPharm Beta). The innovator brand of omeprazole was Losec, produced by AstraZeneca.

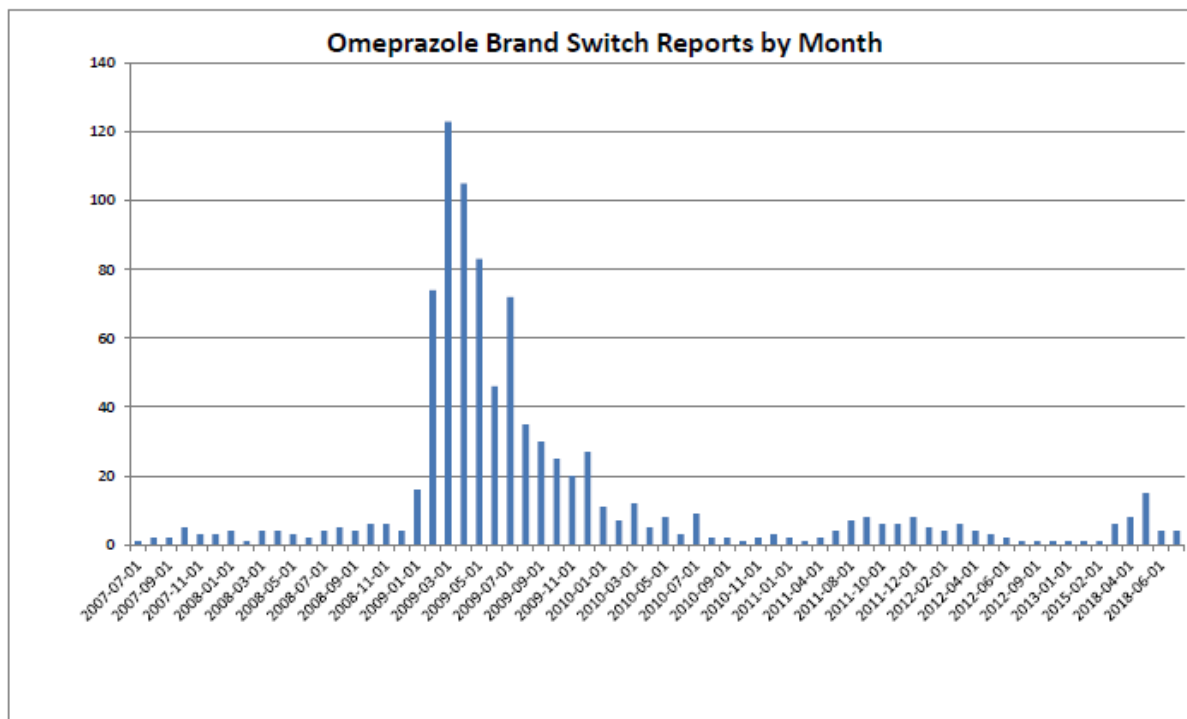
On 1 May 2009, Pharmac ceased subsidy for Losec (as well as subsidised Omezol) and gave Dr Reddy's sole supply for oral omeprazole in New Zealand. Pharmac notified the public of the decision one year beforehand, to give sufficient time to review the medication and gain understanding of the switch. The announcement included changes in the medicines appearance, as well as reassurance on the quality and safety of the new brand, as had been evaluated by Medsafe at the time.

There was widespread media attention for this brand switch, likely due to the high number of people (some sources stating 600,000) taking Losec at the time (6, 27). There was also statements made by AstraZeneca stating that some people used to using Losec could suffer side effects by changing to a generic version. Pharmac labelled this as scaremongering tactics as the new brand was approved as generic medicines by Medsafe (28). There was also scepticism around the product due to its manufacturing site being in India, which was seen by the public to not be up to standard, despite meeting international GMP requirements.

The funded brand of omeprazole later switched to Mylan (Omezol relief) in 2011, and more recently, Actavis. Neither of these switches garnered media attention like the swap from Losec. Consequently, reporting rates of ADRs associated these switches have been significantly lower.

3.1.5.1 Reporting trends

Figure 7: Number of ADR reports for omeprazole coded with “brand switch” received by CARM per month (n=895)



A total of 895 reports have been received by CARM where an ADR has been associated with a brand switch. The major peak observed in figure 7 is in the months around the switch from Losec to Dr Reddy's (funding for Losec ceased in May 2009). The absolute number of reports received during this peak, and overall, is higher than any other switch that is reviewed in this paper. Secondary peaks can be seen in 2011, when the brand switched again to Omezol Relief, and in 2018, when the brand switched to Actavis. These peaks are comparable in size to other brand switches, but are insignificant in comparison to the peaks of the 2009 switch.

The most commonly reported adverse reactions were of the gastrointestinal disorders SOC (n=246, 29.1% of total reports). This included diarrhoea (n=41), dyspepsia (n=15), flatulence (n=18), nausea (n=58) and vomiting (n=11), among others. Rash (n=12), chest pain (n=10) and headache (n=25) were reactions of other SOC categories that had a higher number of reports. 40% of reports (n=359) indicated that the medicine was either ineffective or the therapeutic response had decreased while 15 reports indicated the new brand had aggravated the condition. A mean of 1.72 (median=1) terms were reported each time.

Table 5: Age and sex distribution of reports received by CARM of omeprazole coded with brand switch (n=895)

	Male	Female	Unknown	Total
Unknown	7	8	3	18
<6m	3	4		7
06-23m	2	6		8
02-05y	1	4		5
06-11y		3		3
12-16y		1		1
17-29y	2	3		5
30-39y	9	6		15
40-49y	30	39		69
50-59y	62	113		175
60-69y	102	289		391
70-79y	80	141		221
80+	10	10		20

Table 5 shows the age and sex distribution of the reports. Reports are primarily clustered in the higher age groups, as expected by the population that primarily uses this medicine. There is also a slightly higher number at the infancy and early childhood range, where this medicine is used to treat gastric reflux in infants and children.

The number of reports from females are significantly higher than that of males in the age brackets where increased reporting is observed, with the exception of 80+.

Comments

This was the first brand switch following the Eltroxin formulation change (see section 5) that garnered a lot of attention. Public knowledge of CARM was high following the controversy, potentially leading to high reporting rates for omeprazole as people understood the channels for reporting their reactions.

3.1.6 Venlafaxine

The switch to the sole subsidy of the Enlafax brand of venlafaxine has been a large source of attention and controversy over the last year. Venlafaxine is an antidepressant, in the serotonin-noradrenaline reuptake inhibitor class (SNRI). Its short half-life (5-11hours) has required it to be formulated as an extended release formulation. It is also notably prone to discontinuation symptoms, which can include agitation, anxiety, fatigue, nausea, dizziness, headaches and others (29).

The innovator brand of venlafaxine, Efexor, was first approved by Medsafe in 1993 and has been the utilised brand of this medicine for many patients who require it. Arrow Venlafaxine was approved in 2010 and has since gained subsidy, however was not awarded sole supply, allowing patients to remain on Efexor. Arrow Venlafaxine was also a tablet formulation, giving it a significant difference in appearance compared to Efexor.

Enlafax gained subsidy from April 2017 and the subsidies for Efexor and Arrow were removed by September 2017, giving Mylan sole supply for venlafaxine in New Zealand. Pharmac provided extensive information on this brand switch including information sheets for health professionals, changes in appearance of the tablets/capsules and assurance that Enlafax works identically to the previously subsidised brands.

In February 2018, the brand switch started gaining considerable media attention. The New Zealand Herald initially published an article highlighting the experiences of some patients (30). A Facebook page, named *The Nutters Club*, was also highlighted as a source where patients had been discussing their experience with Enlafax. The Herald interviewed one person in particular, Heather Williams,

who has since become a leading figure in the movement for Pharmac to reinstall subsidy of Efexor. More articles in the media were continued to be published (31, 32).

Additionally, a petition was made to Health Minister, David Clarke, and Professor David Menkes, requesting that the House of Representatives urge Pharmac to increase the access to Efexor for patients who cannot tolerate Enlifax. The core complaints was that the current NPPA process was too restrictive to get exceptional funding and endangered vulnerable people's health and wellbeing.

Comments

Although Medsafe's quality and safety assurance was initially brought into question, the focus of the campaigners has appeared to switch to targeting reinstatement of funding for Efexor, rather than removal of Enlifax. This appears to be due to an understanding that there are no issues with Enlifax; rather there is a small minority of people who have not tolerated the new brand for a variety of reasons. This is evident in the statements made in two different petitions (the web platform was changed to ensure it reached the Minister):

*We need to make sure our [Minister of Health](#) and those who are invested in ensuring that "medicines and medical devices have acceptable efficacy, quality and safety" ([MedSafe](#)) are made aware of this issue and **TAKE ACTION** to safeguard those at risk.*

Compared to

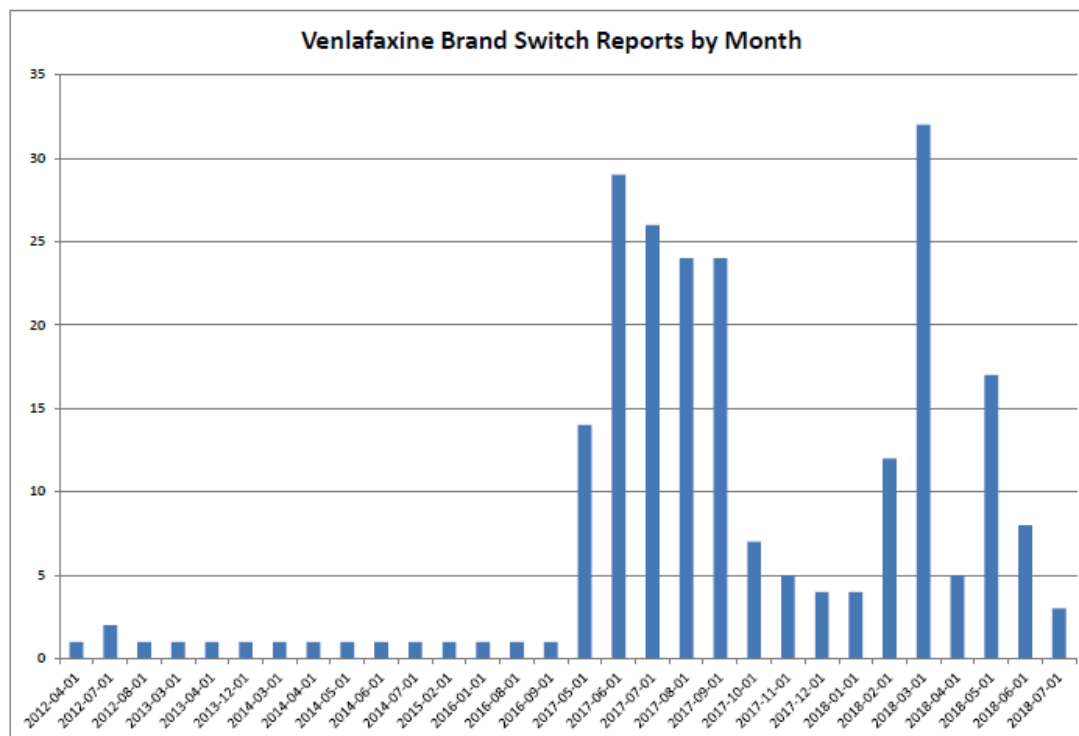
That the House of Representatives urge Pharmac to make it easier for patients who have severe adverse effects when taking generic medication to be funded for brand-name medication.

The issue is on-going and the petition is still active for signing. At the point of writing, there have been no changes or regulatory action. Medsafe has confirmed the bioequivalence data for Enlifax and assured Pharmac that there are no quality issues. Pharmac has stated they would consider changing the funding if Medsafe deemed there was a change to the risk benefit of Enlifax.

3.1.6.1 Reporting trends

A total of 230 reports have been received by CARM of ADRs associated with brand switches for venlafaxine. Multiple major peaks can be observed as per figure 8. The first is around the time the brand switch occurred, in September 2017. This peak is in line with other brand switches and the increase reporting rate can be considered expected. However, as this peak tapers off in a similar fashion to other brand switches, a second peak occurs in March 2018. This peak is directly following the media stories published at the end of February 2018. The media attention likely stimulated increased reporting of the issue. Another, minor peak, can be seen in May, when the petition was created. The trend between then and the present time indicates the report numbers are tapering off. This pattern is dissimilar to that of other brand switches, but can be easily attributed to the media attention and widespread publicity at various points in time.

Figure 8: Number of ADR reports for omeprazole coded with “brand switch” received by CARM per month (n=230)



Reported terms were varied, with major SOCs being Central and Peripheral Nervous System Disorders (n=27, 11.7%) and Psychiatric Disorders (n=28, 12.2%). The most commonly reported terms were dizziness (n=6), headache (n=11) and nausea (n=6). These are all non-specific terms that are commonly reported with brand switches, as evident when comparing the switches reviewed in this paper. Some reports have indicated severe symptoms such as suicidal ideation (n=5), thoughts of self-harm (n=1), suicide attempt (n=1), depersonalization (n=1), hallucination (n=1), depression (n=3) and emotional lability (n=2). Nine reports specifically indicated a drug withdrawal syndrome/withdrawal syndrome, and multiple other reports reported symptoms that could also be associated with venlafaxine withdrawal. 33.9% of reports indicated the therapeutic response was decreased. A mean of 2.33 (median=2) terms are reported each time.

The age and sex distribution of reports is shown in table 6. The reports vary in age with a peak at 40-49 years of age. Women have been predominantly affected by the brand switch, reasons for this cannot be concluded. However, the usage data of venlafaxine shows that the largest users of venlafaxine, since 2014, are women aged 40-49. Additionally, the ratio of female to male users has consistently been approximately 1.8 since 2014. The observation that reporting trends reflects usage data suggests that high use groups can be expected to be a major source of reports, as expected. This could be used to target interventions.

Table 6: Age and sex distribution of reports received by CARM of venlafaxine coded with brand switch (n=230)

	Male	Female	Unknown	Total
Unknown	2	2		4
16-29y	2	15		17
30-39y	11	36		47
40-49y	14	54		68
50-59y	8	37		45
60-69y	15	24		39
70-79y	4	3		7
80y+	0	3		3

4.0 REPORTER TRENDS

An analysis of the reporters can provide useful insight into targets for interventions to improve public safety with brand switches. Figures 9-15 show the number of reports received by either a GP, pharmacist, or where relevant, a member of the public, over months where a high number of reports were made of reactions associated with a brand switch. Hospital doctors, companies, nurses, and others, made an insignificant number of reports in comparison to pharmacists and GPs. The exception to this is for methylphenidate, where a number of hospital-based specialists reported adverse effects.

Figure 9: Number of reports of ADRs associated with a brand switch received per month, grouped by reporter type for methylphenidate (n=83)

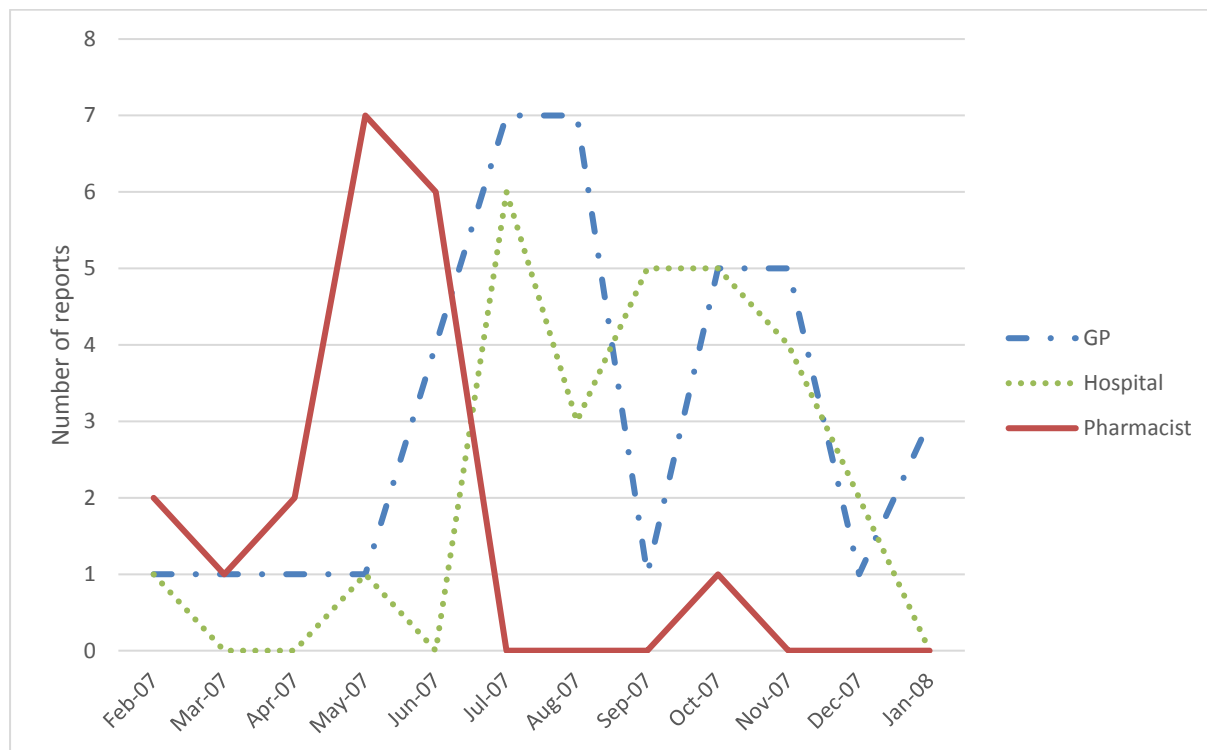


Figure 10: Number of reports received of ADRs associated with a brand switch per month, grouped by reporter type for enalapril (n=31)

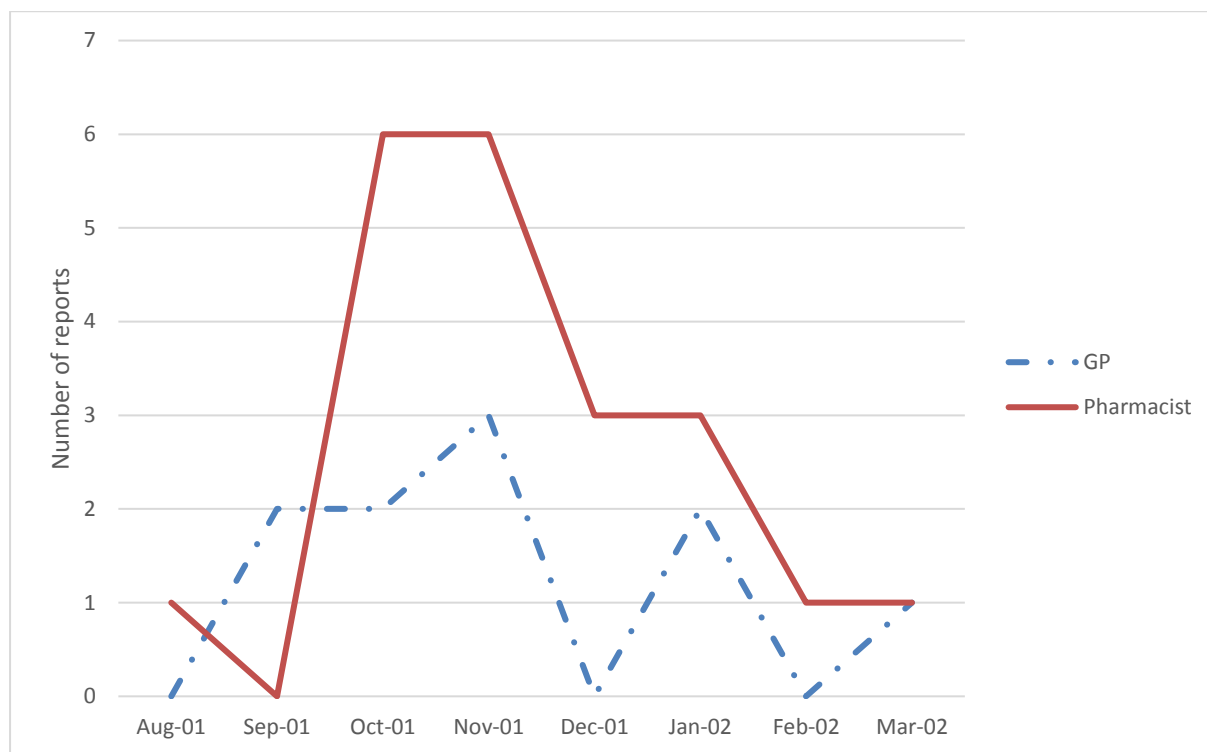


Figure 11: Number of reports of ADRs associated with a brand switch received per month, grouped by reporter type for simvastatin (n=111)

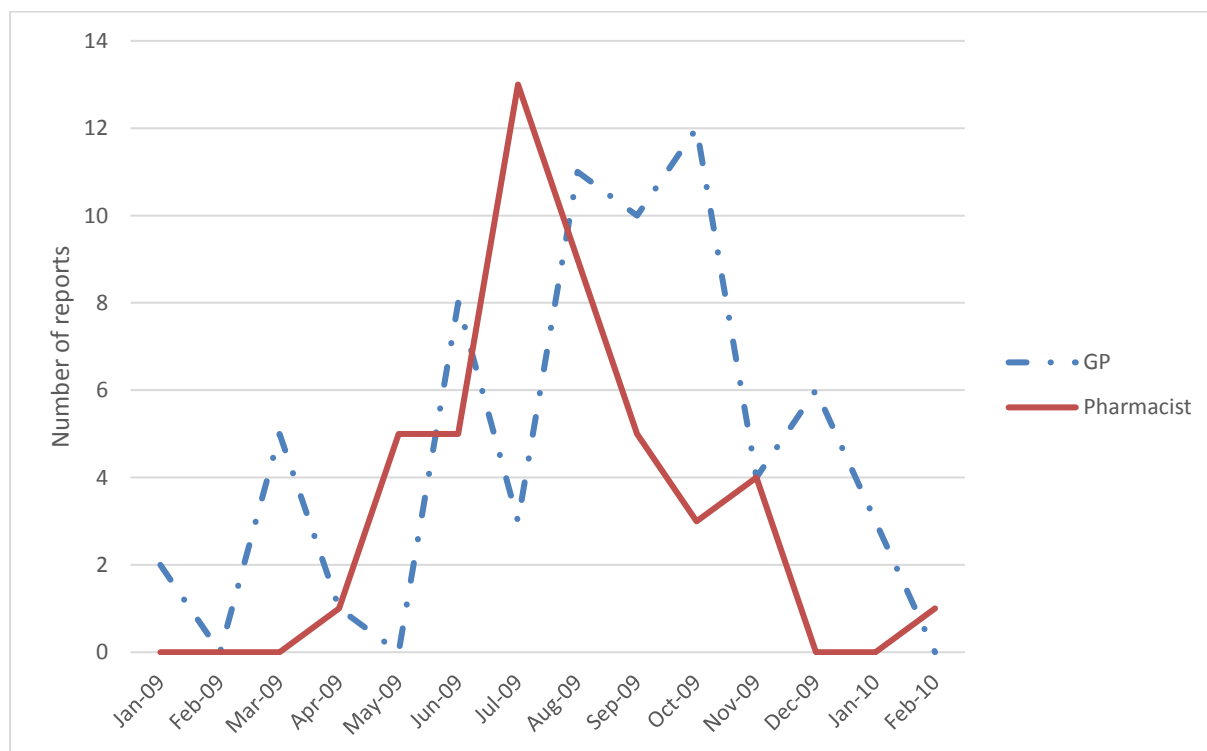


Figure 12: Number of reports of ADRs associated with a brand switch received per month, grouped by reporter type for fluoxetine (first switch) (n=48)

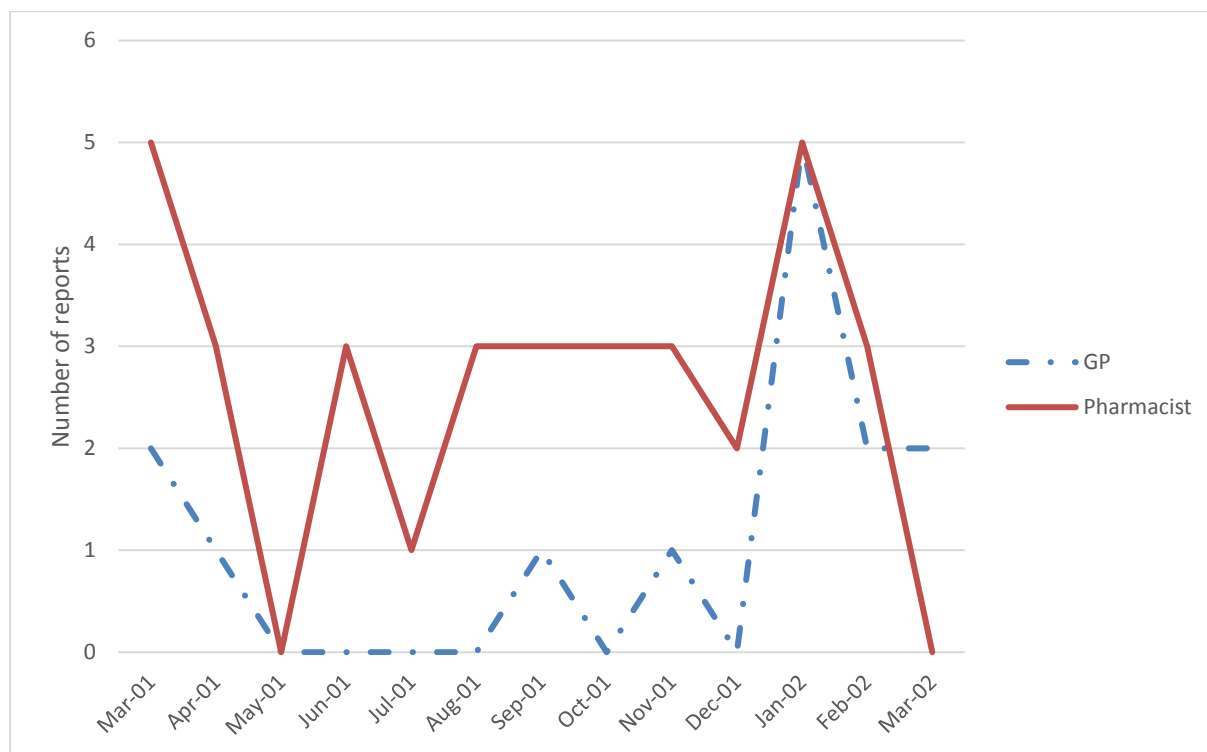


Figure 13: Number of reports of ADRs associated with a brand switch received per month, grouped by reporter type for fluoxetine (second switch) (n=17)

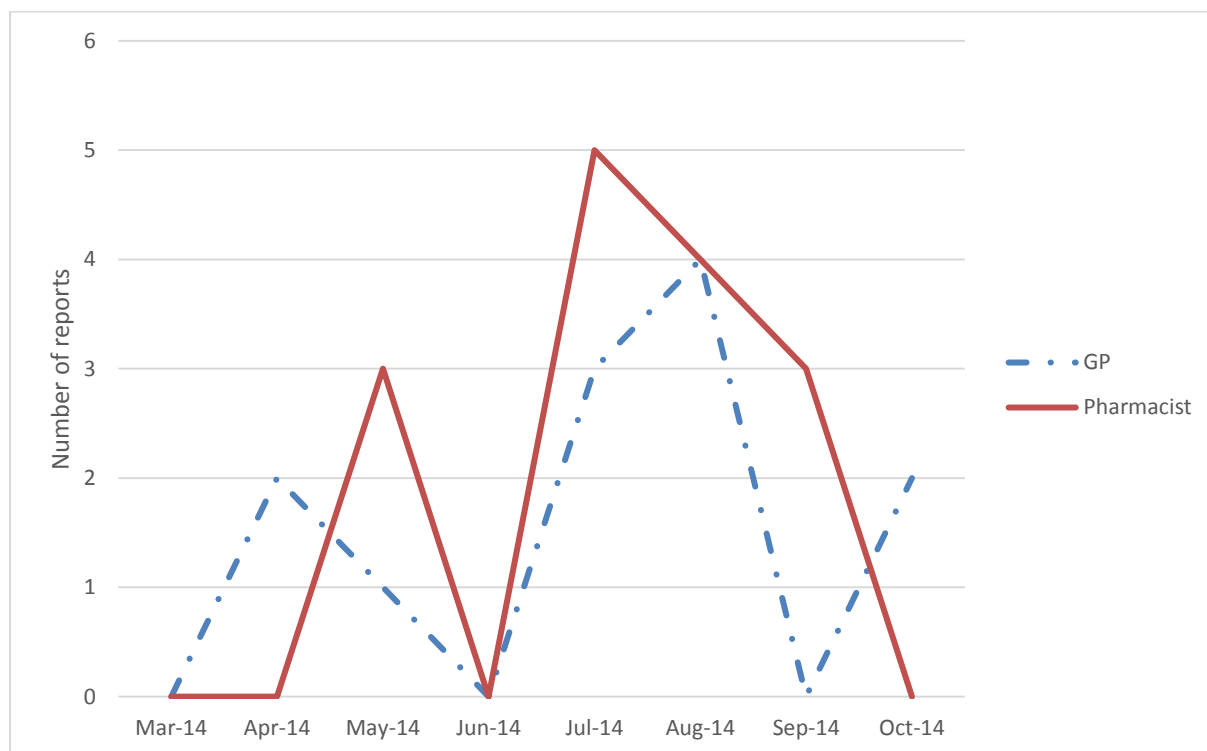


Figure 14: Number of reports of ADRs associated with a brand switch received per month, grouped by reporter type for omeprazole (n=654)

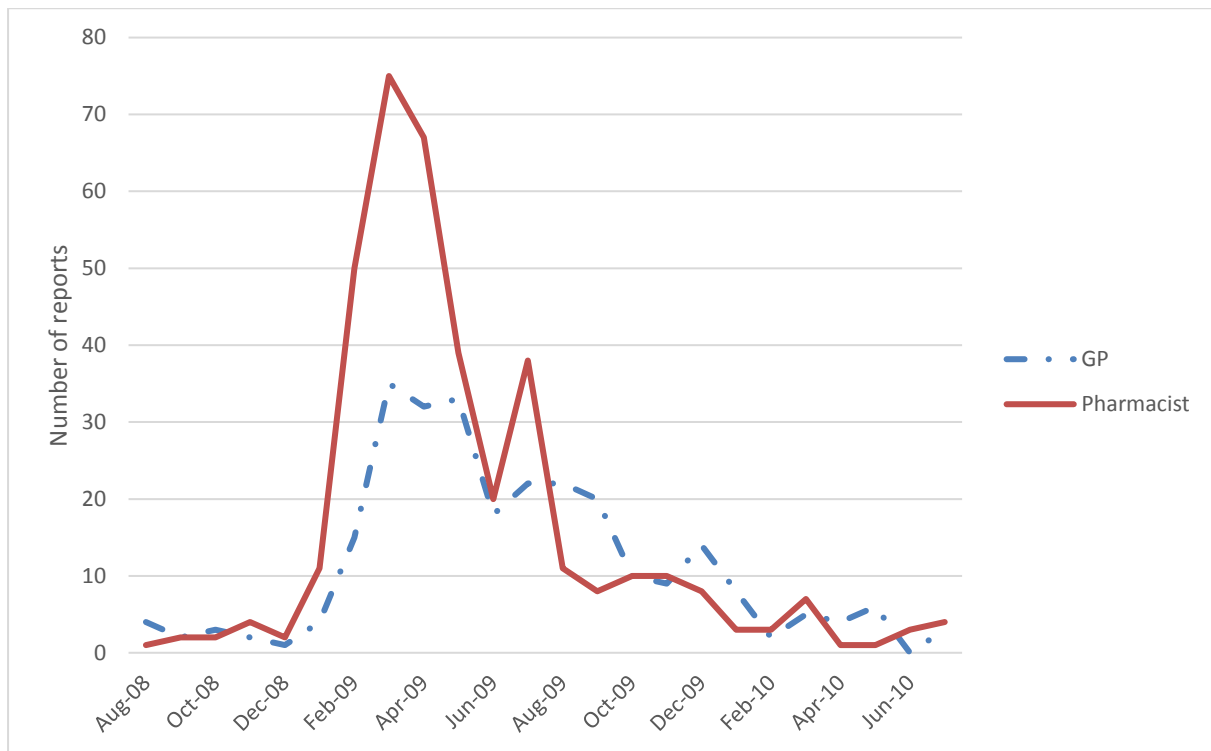
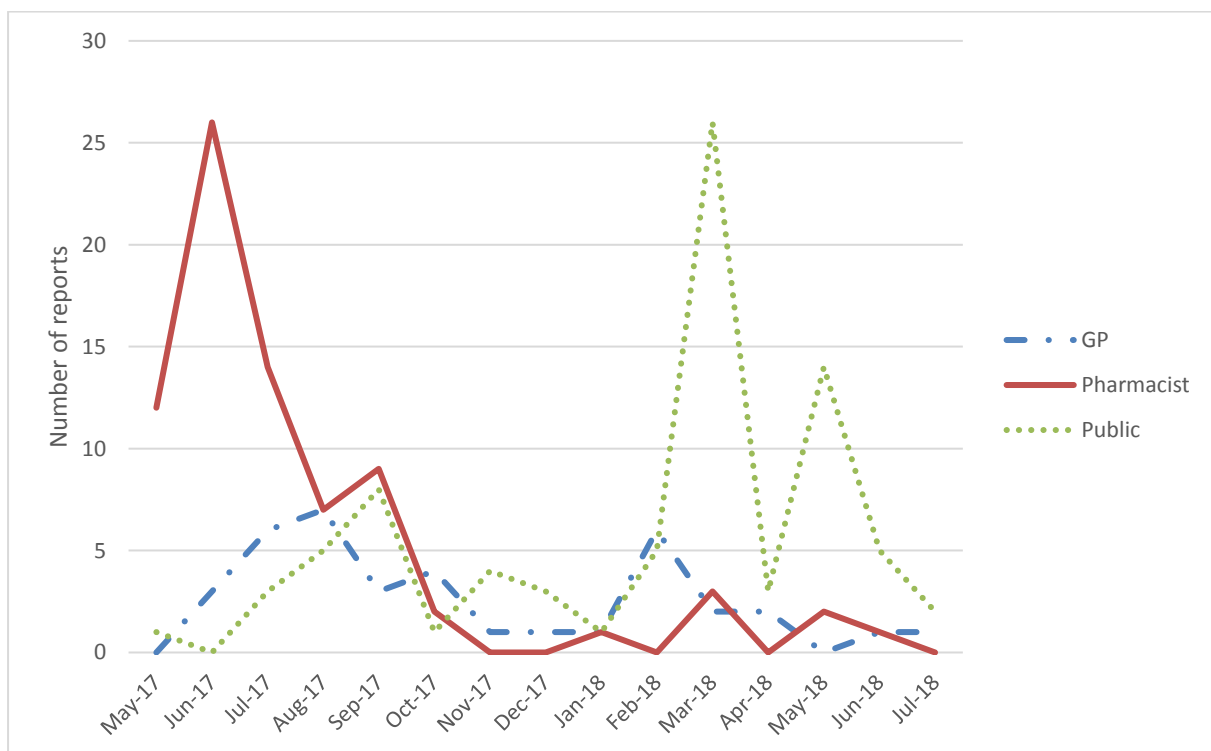


Figure 15: Number of reports of ADRs associated with a brand switch received per month, grouped by reporter type for venlafaxine (n=196)



The figures indicate that pharmacists are often the first group to begin making these types of reports; GPs generally start reporting later. Both groups make a significant number of reports and should be targeted for intervention. Consumer reporting was a major factor in the venlafaxine brand switch. There was no consumer reports made for omeprazole, despite the Eltroxin switch (see

section 5), which increased public awareness of CARM and ADR reporting, occurring just two years prior. There are a number of potential explanations for these trends; some are highlighted below.

- Pharmacists interact with patients at the point of dispensing, leading to queries/complaints about new brands being directed at pharmacists.
- Pharmacists interact with the patient at the second dispensing when he/she has tried the medicine and suffered an adverse effect. This can occur prior to the next scheduled GP appointment.
- Pharmacists are more accessible than doctors for patients to discuss adverse reactions, especially if the reaction is mild.
- Pharmacists are more likely than GPs to establish a relationship between a brand switch and an adverse reaction – GPs may not even be aware the brand switch has occurred.
- GP reporting rate remains high as patient's with adverse reactions to medicines need to be referred to their GP for any changes – pharmacists cannot make any changes themselves (other than swap to an alternate brand if available).
- GP reporting is higher later in the brand switch period as they would only see their patients every 3 months for refill prescriptions – they would not be aware an adverse reaction has occurred until the patient comes in for an appointment.
- Consumer reporting for venlafaxine shows spikes directly following the release of news articles and the petition. This shows that the media can have a strong effect on consumer reporting in modern trends.

5.0 ELTROXIN FORMULATION SWITCH (33)

Hypothyroidism is a common medical disorder that is easily managed by replacement treatment with synthetic thyroxine. About 70 000 New Zealanders have hypothyroidism and are treated with thyroxine replacement medication. Since 1973 the only thyroid hormone replacement drug approved and funded by the government for use in New Zealand was the Eltroxin brand, made by GlaxoSmithKline. In 2007 the company moved the manufacture of Eltroxin from Canada to Germany. This resulted in a change in the tablets' inert ingredients: the new formulation differed in markings, size, and colour and—according to some reports—also in taste and rate of dissolution on the tongue. The active ingredient (thyroxine) remained unchanged and continued to be made in Austria. The new formulation was approved by Medsafe (33).

In 2007 and 2008 New Zealand pharmacies changed to the new formulation of Eltroxin. The old formulation had been used for more than 30 years without problems; but after the new tablets were introduced the rate of adverse event reporting rose nearly 2000-fold—from 14 reports in 30 years to more than 1400 in 18 months (33).

Adverse reaction reports relating to the new formulation were first received in October 2007 by New Zealand's Centre for Adverse Reactions Monitoring, CARM. By July 2008, 294 incidents of adverse reactions had been reported—most (251) reports were received after the Eltroxin formulation change hit the press. The number of adverse reaction reports peaked in September 2008 (at 492). The number fell in October that year to 177 and even further in November to 21, after an announcement that an alternative thyroxine brand was being approved.

About half of all the symptoms reported—such as weight gain, lethargy, muscle pain, joint pain, and depression—can be features of hypothyroidism, but other commonly reported symptoms are not: conjunctivitis, eye pain, headache, itching, skin rash, abnormal or blurred vision, nausea, and indigestion. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) consulted with local endocrinologists and sought information from the 30 countries in which the new formulation of Eltroxin is used. Some countries reported a small increase in the number of adverse reports, but none had such a dramatic increase as in New Zealand. Medsafe also had independent tests conducted, which found that the new formulation contained the ingredients listed by the

company, had the same levels of thyroxine as the old formulation, and was bioequivalent to the old tablet.

Medsafe issued a press releases to clarify misinformation being spread through the media and internet sites about the new Eltroxin formulation. This misinformation included rumours that the new formulation was being manufactured in India and contained genetically modified ingredients and monosodium glutamate.

In response to public pressure two additional brands of thyroxine were approved for use in New Zealand in October 2008, enabling patients to switch brands without additional expense. Although these alternatives were provided as soon as they could be, the public perception was that Medsafe's response to the adverse reactions reporting was too slow, as reflected by demands for immediate action from politicians in a press release headed "How long will Eltroxin sufferers have to wait?" By April 2009 the level of adverse reaction reporting had dropped back to nearly that before the formulation change and has remained low since. There have been very few media stories about the formulation change since November 2008. Despite the negative publicity about Eltroxin, data from Pharmac indicates that as of June 2009, many patients had gone back to the drug and about 80% of patients using thyroxine were taking the new formulation of Eltroxin.

The following two studies investigate this change from psychological and sociological viewpoints. Although this was not a brand switch, the studies provide an interesting perspective on the role that media, public reactions and governmental agencies play. These studies provide valuable insight from a different lens and also draw parallels to brand switches, highlighting areas that can be targeted for future improvement.

5.1.1 Gardner & Dew, 2011 (34)

This study uses the Eltroxin formulation switch to investigate the use of the Actor-Network Theory (ANT) in sociological studies. Although ANT is not relevant to this paper, the observations this study presents on the Eltroxin switch can be utilised to understand different forces in play during a brand switch, and how that can affect ADR reporting and patient outcomes.

The paper follows the events, noting when important changes occur and how they affect future events and the end outcome.

1. A sufferer of hypothyroidism, Lyn, made a link between her new symptoms and her new medicine after listening to people with the same problems discussing this on talk back radio. The radio provided the initial means for an otherwise discrete collection of individuals to form a group bound by the belief in the ill-effects caused by the new formulation.
2. *The Southland Times* published a story on this potential link, further disseminating the nascent groups rendering of the medicine to a wider audience. The article included discussions about Medsafe, Pharmac and GSK's role. The newspaper drew a series of associations between bodily symptoms of Lyn, Eltroxin, and GSKs manufacturing processes in Germany.
3. Due to Lyn's phone number being published in the article, she claimed to have received "hundreds" of complaints from people having the same symptoms. This prompted *The Southland Times* to publish another article which elaborated on the alternative medication (Goldshield brand) taken by Lyn that doesn't cause any side effects. This article reaffirmed to the readership the series of associations made in the first article.
4. The article prompted patient's to report their adverse reactions to CARM. It provided instructions to Eltroxin users, attempting to channel one series of actions into another series of actions. It encouraged the translation of anecdotal complaints of a group of dispersed individuals into coordinated and homogenous action by contacting CARM.

5. *The Waikato Times* also published an article after someone in the Waikato region experienced problems, exposing the controversy to 40,000 more people. Media coverage continued and increased, exposing the problems to more people.
6. A massive flow of reports was received by CARM, of which 40% were consumer reports. CARM became a voluntary passage point, where the actions of dispersed individuals were coordinated into a series of formal reports. They essentially acted as an inscription device, translating scattered action among members of the population into a format that could be subject to various statistical analyses. It produced an official appraisal of risk.
7. Medsafe issued statements saying the formulation had been retested and GSK ordered to issue information concerning the medicine directly to consumers. The statements also suggested that poor patient compliance should be considered as a possible cause of adverse effects. In doing this, Medsafe became delineated and engaged in action that induced other actors to delineate themselves.
8. Allan Campbell, a Temuka-based pharmacist, claimed that Medsafe, along with other government agencies has failed to react with sufficient haste. Support groups formed which criticised the government and requested subsidies of the Goldshield brand of levothyroxine. Opposition MPs also claimed ineffectiveness of the Government and Medsafe. These actions strengthen the viewpoint that the new Eltroxin formulation was the cause of the adverse reactions. As more individuals, groups, and agencies become enrolled in this viewpoint, it becomes more factual and has a greater ability to induce entities to delineate themselves and act, as well as becoming more durable and difficult to dismiss.
9. As more politicians became entwined, only one out of the two viewpoints that had been originally expressed, had been disseminated with any success. Very few people and groups had taken the position that Medsafe was correct, regardless of the absolute truth. CARM and Medsafe were restricted to a monitoring role. The success of the anti-Eltroxin group is best indicated by the media coverage.
10. Medsafe and CARM provided information to MARC. The recommendations from the Committee meeting represented a further translation of action: the summary of adverse reaction reports composed by CARM, and the worldview constructed by Medsafe have prompted the Committee to act and to initiate activities that will put other actors into motion.

The media was vital: it disseminated the rendering of Eltroxin as the cause of adverse reactions, the risk, to a very large readership. Importantly, it enabled an otherwise diverse heterogeneous collection of dispersed individuals to group together behind various spokespeople. It also coordinated this group by illustrating a conduit for action: the media provided details of CARM and encouraged sufferers to report their symptoms. It therefore facilitated a widespread, concerted response to risk.

By reporting directly to CARM, sufferers could bypass the usual channel for reporting to GPs, who may be both placating and dismissive. Consequently, CARM received a large quantity of reports which were standardised through CARMs various ordering and sorting practices. Politicians acted as another conduit for action: the complaints of the worried, anxious individual became the basis for political sound bites and rhetoric.

5.1.2 Faasse, Cundy & Petrie 2009 (33)

The authors of this study discuss four major factors which they believe had roles in causing the massive amounts of reports received by CARM.

- External factors – at the time of the formulation switch, Pharmac was under intense scrutiny due to decisions made around rationing the availability of Herceptin to only early stage breast cancer. Patients saw the formulation change as a cost cutting strategy by Pharmac,

despite the newer formulation being more expensive. The negative perception and distrust of Pharmac from this are likely to have contributed to the problems.

- Champions – Alan Campbell, a pharmacist from Temuka, publicised patients' concerns by giving media interviews. This brought the issue to the attention of the public, but also created fear and dissatisfaction that may have made the situation worse. There was also appeal in his position as a small town health professional taking on the “medical establishment”.
- Media coverage – Media coverage of the issue was widespread, but varied between regions. The intensity of the coverage was related to the rates of ADR reporting, showing the strong effect the media can have on ADR reporting rates and potentially the development of nocebo-based symptoms. In the Auckland region, where the news media did not particularly focus on the story, is home to around 31% of the New Zealand population but accounted for only 16% of all adverse reactions reported. In contrast 41% of all adverse reaction reports came from the Bay of Plenty, Canterbury, and Southland regions, which together have only 22% of New Zealand's population. The Eltroxin story was covered extensively in local newspapers in these regions.
- Patient factors – Hypothyroid patients, even those taking thyroxine replacement therapy, had been found to have higher levels of emotional stress and more physical symptoms than people without hypothyroidism. Because of this, they are more likely to attribute physical symptoms to a medical intervention or illness. It is likely that patients taking Eltroxin misattributed unrelated physical symptoms to the new formulation. Additionally, they may have misattributed indications that they required a re-evaluation of their dose as instead being harmful adverse effects.
- Although the authors did not consider this a separate factor, social media attention is discussed. Internet support groups and chat forums provided channels for false rumours to be spread about the drugs manufacture, ingredients, and the agenda of the “medical establishment”. The misinformation may have influenced patients' beliefs and expectations about the likelihood of experiencing physical symptoms in response to the formulation change and also to the spread of physical symptoms in these patients.

6.0 DISCUSSION AND CONCLUSIONS

Brand switches will continue to happen in New Zealand due to the function of Pharmac and the increasing number of generics on the market. Pharmac aligns with international consensus in the economic benefit of generic medicines, however it is apparent from reporting trends that there is a risk of adverse drug reactions when brand switches occur. Currently, Medsafe acts in a retroactive manner to brand switches, where increased reporting encourages reviews of the medicine, media statements and public assurance of safety and quality. Thus, there lies an opportunity to take on a more proactive approach, using general and targeted risk minimisation interventions to enhance public safety, reduce the potential for harm and improve public trust in Pharmac, Medsafe, and the wider government.

On a New Zealand population-level, there is no evidence of issues with brand-switches (35). This is in line with international evidence on the effectiveness and economic benefits of generic medicines. The ADRs that are reported appear to be on an individual level and the causative mechanisms of such ADRs can be difficult to pin point. In the eye of public safety, exploring ways in which Medsafe can approach brand switches to reduce adverse reactions has become important, especially in light of the recent issues with Enlax (venlafaxine).

The ADRs that occur are likely not of any physiological mechanism, or due to pharmacological properties of the medicine. Theories as to how these come to be may be through negative

perceptions and the nocebo effect – where the simple knowledge that the brand has changed may lead to adverse effects. An alternate explanation is that disease-related or non-related symptoms are being attributed to adverse effects associated with the brand switch – these are not true ADRs but are reported and treated as being ADRs. There are rare situations where a patient may have an intolerance to a changed excipient, however these would not be expected to occur at the observed rates.

The media has been shown to play an increasingly important role in the reporting trends. In the early 2000s, brand switches generated ADR reports, but at a much lower number in comparison to recent switches. News was less accessible than it currently is, with online media, social media and discussion boards. Since the Eltroxin formulation issues, the media has started publishing more articles highlighting cases where patients state the cause of their adverse reactions are the brand switch. The validity of these articles are irrelevant to the core issue – media portrayal plays an important role in shaping the public's perception of the world and will directly stimulate certain trends. High reporting of venlafaxine ADRs directly following media reports is an excellent example of this effect. If only negative effects are [widely] publicised, there is a higher risk of the nocebo effect or misattribution of symptoms.

Currently, Pharmac releases information on their website about brand switches. These include details of the change, including the appearance of the medicine, who it affects and how they will be affected. BPAC also occasionally writes articles, however these would only reach health professionals. As previously stated, the presence of Medsafe is retroactive and only happens when public backlash has occurred. At that point in time, it is increasingly difficult to ensure the public, especially those who have experienced harm, that the medicine is safe and effective.

As seen with venlafaxine, affected patients correlate with the usage data. Females have almost twice the usage rates of venlafaxine, and are twice (or more) likely to have reported an adverse reaction with the switch from Efexor to Enlafax. Additionally, the highest use group is females aged 40-49, who are also the group with the highest number of reports. Therefore, there may be opportunity to target high use groups with risk minimisation measures; Pharmac information tends to be more general to the whole population of users.

Reporters themselves are an important group to consider. Ultimately, they are the ones who diagnose the adverse reaction, associate the adverse reaction with the brand switch and report the reaction to CARM. Pharmacists are shown to be high reporters of these reactions, especially in the initial periods when the switch occurs. This indicates that pharmacists have early exposure to patients experiencing these reactions. Pharmacist targeted risk minimisation measures may therefore be highly effective. GPs are the second group where reports primarily come from and can also be targeted. Other health professionals do not appear to be exposed to these kinds of reactions.

The third reporting group, that was a major group in the recent venlafaxine brand switch, is the public. These reporters are more difficult to target as they are far more likely to get information from the media than Medsafe or Pharmac. Ensuring that sufficient, reliable information can be found is therefore important in enhancing public knowledge and reducing the risk of harm. As previously discussed, the 2016 survey suggested a very poor public knowledge of brand switches. It is unknown whether this has an effect on ADR reporting, but prompts intervention in this area.

Some suggestions for risk minimisation measures are as follows. The list is non-exhaustive and further recommendations are encouraged.

- **Publishing evaluations of generic medicines** – creating transparency in Medsafe's evaluations of generic medicines would enhance public trust and confidence in Medsafe's capabilities. Additionally, if reactions occur, this can safeguard Medsafe from accusations that information is being hidden. It also enables health professionals to access this information and relay it in consultations to their patients.

- **Medsafe communications on the website** – proactive communications with the public can reduce the risk of negative perception formation. The information can be used by health professionals, alongside Pharmac communications, to ensure patients are fully informed about the change in brands.
 - Important generic medicines to target (if not all) would be medicines used in psychiatry, medicines with very high usage, and generics that would replace the innovator product.
- **Communication to Pharmaceutical Society and College of GPs** – sufficient patient education and counselling provided by these two groups may reduce rates of ADRs. Counselling at the points of dispensing is likely to be more beneficial, as pharmacists can give a complete explanation, show the patient the medicine, provide assurance of its quality and safety, and answer any questions the patient has. Input from the GP when prescribing would also be beneficial in conjunction with this. If the patient has a positive perception of the brand change, they are less likely to suffer an ADR.
- **Include brand switches in *Prescriber Update* when necessary.**
- **Consumer information leaflet on brand switches (general scope).**
- **Referring select generic medicine applications to the MAAC** – an audit from a Ministerial advisory Committee will provide additional evidence to the safety and efficacy of generic medicines when this is questioned by the public.

7.0 ADVICE SOUGHT

The Committee is asked to advise on where Medsafe can create risk minimisation measures to enhance public safety, improve public trust in Medsafe, Pharmac and the wider government, and reduce the potential for harm from adverse drug reactions associated with brand switches.

8.0 ANNEXES

1. Signal detection and evaluation in New Zealand, Report for MARC June 2009
2. Guideline on the Regulation of Therapeutic Products in New Zealand, Part 6: Bioequivalence of medicines
3. EMA Guideline on the Investigation of Bioequivalence
4. EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms

9.0 REFERENCES

1. Food and Drug Administration. 2018. Generic Drug Facts.
2. Food and Drug Administration. 2015. Generic Drug Savings in the U.S. In *Washington, DC: Generic Pharmaceutical Association (GPhA)*
3. BPAC. 2009. Generics Special Edition. In *Best Practice Journal New Zealand*
4. World Health Organization. 2016. *WHO Guidance for organizations performing in vivo bioequivalence studies.*
5. Saul S, Berenson A. 2007. Maker of Lipitor Digs in toe Fight Generic Rival. In *New York Times: The New York Times Company*
6. Scoop Media. 2008. Stark choice for around 640,000 Kiwis.

7. Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK, Shrank WH. 2008. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *Jama* 300: 2514-26
8. Corrao G, Soranna D, Arfè A, Casula M, Tragni E, Merlino L, Mancina G, Catapano AL. 2014. Are generic and brand-name statins clinically equivalent? Evidence from a real data-base. *European journal of internal medicine* 25: 745-50
9. Corrao G, Soranna D, Merlino L, Mancina G. 2014. Similarity between generic and brand-name antihypertensive drugs for primary prevention of cardiovascular disease: evidence from a large population-based study. *European journal of clinical investigation* 44: 933-9
10. Desai RJ, Sarpatwari A, Dejene S, Khan NF, Lii J, Rogers JR, Dutcher SK, Raofi S, Bohn J, Connolly J. 2018. Differences in rates of switchbacks after switching from branded to authorized generic and branded to generic drug products: cohort study. *bmj* 361: k1180
11. Desmarais JE, Beauclair L, Margolese HC. 2011. Switching from brand-name to generic psychotropic medications: a literature review. *CNS neuroscience & therapeutics* 17: 750-60
12. Medicines and Healthcare products Regulatory Agency. 2014. Antiepileptic drugs: new advice on switching between different manufacturers' products for a particular drug In *Drug Safety Update*
13. Andermann F, Duh MS, Gosselin A, Paradis PE. 2007. Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. *Epilepsia* 48: 464-9
14. Brazil R. 2018. Nocebo: the placebo effect's evil twin. *The Pharmaceutical Journal* 300: 05
15. Abramson JD, Rosenberg HG, Jewell N, Wright JM. 2013. Should people at low risk of cardiovascular disease take a statin. *Bmj* 347: f6123
16. Nikiphorou E, Kautiainen H, Hannonen P, Asikainen J, Kokko A, Rannio T, Sokka T. 2015. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. *Expert opinion on biological therapy* 15: 1677-83
17. Tinnermann A, Geuter S, Sprenger C, Finsterbusch J, Büchel C. 2017. Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science* 358: 105-8
18. PHARMAC. 2018. About PHARMAC.
19. Lessing C, Ashton T, Davis P. 2016. New Zealand patients' understanding of brand substitution and opinions on copayment options for choice of medicine brand. *Australian Health Review* 40: 345-50
20. England S. 2006. Brand change for ADHD medication. PHARMAC
21. Johnson M. 2007. Drug switch plunges boy into hell. In *The New Zealand Herald*
22. Medsafe. 2007. Minutes of the 131st Medicines Adverse Reactions Committee Meeting.
23. Medsafe. 2002. Minutes of the 111th Medicines Adverse Reactions Committee.
24. Zealand MN. 2018. Simvastatin Mylan New Zealand Data Sheet.
25. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, Watanabe N, Nakagawa A, Omori IM, McGuire H. 2009. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *The lancet* 373: 746-58
26. BPAC. 2014. Fluoxetine brand change: Arrow Fluoxetine sole subsidised brand from 1 July. *Best Practice Journal New Zealand* 61

27. Radio New Zealand. 2008. Pharmac opts for generic version of Losec.
28. NZPA. 2009. Pharmac defends decision to drop Losec. In *Stuff*
29. Mylan. 2018. New Zealand Data Sheet: Enlifax XR
30. Henry D. 2018. Patients say Pharmac-funded version of antidepressant venlafaxine left them depressed, anxious. In *The New Zealand Herald*
31. Steele M. 2018. Fight over Pharmac's switch to generic anti-depressant brand continues. In *Stuff*
32. Maude S. 2018. Anti-depressant swap: Sufferers claim generic drug is harming their condition. In *Stuff*
33. Faasse K, Cundy T, Petrie KJ. 2009. Thyroxine: anatomy of a health scare. *Bmj* 339: b5613
34. Gardner J, Dew K. 2011. The Eltroxin controversy: Risk and how actors construct their world. *Health, risk & society* 13: 397-411
35. Lee C. 2015. *Reference pricing and health outcomes: Evaluating the impact of generic substitution in New Zealand*. The University of Auckland. 171 pp.