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Reference pricing and health outcomes: Evaluating the impact of
generic substitution in New Zealand

Charon Lessing

A thesis submitted in fulfilment of the requirements for the degree of Doctor of
Philosophy, The University of Auckland, 2015.
Abstract

Background

A fundamental predicament faced by healthcare policy makers is balancing access to the most effective and oftentimes expensive medicines whilst containing total pharmaceutical expenditure; meeting the health needs of the individual, yet not at the expense of society.

New Zealand’s Pharmaceutical Management Agency (PHARMAC) has consistently kept expenditure on community pharmaceuticals within budget, employing pharmacoeconomic technology assessments and a mix of pricing strategies to achieve this. However, the advent of complex, biologically-derived, expensive pharmaceuticals has commenced and the population is increasingly weighted with an elderly, medicine-consuming sector. These factors will challenge PHARMAC’s ability to contain pharmaceutical expenditure.

As patented medicines come to the end of their exclusivity period and generic equivalents become available, opportunity exists for considerable savings to be made by purchasing generics or using the price of the generics as leverage. This ‘generic reference pricing’ is the simplest form of benchmarking strategies used by funders such as PHARMAC; and will be a valuable tool in providing access to expensive biopharmaceuticals in the future. However, it necessitates switching between different brands of medicines, and as evidence of the safety of this practice is limited, resistance to it exists amongst health professionals and patients alike.

Aims

This thesis tested the hypothesis that patients who switch from an originator brand to a generic equivalent medicine fare no worse than those who do not make a switch.

The objectives were: firstly, to measure patient health outcomes consequent to the implementation of generic reference pricing and any associated change in costs; and secondly, to explore the perspective of patients affected by brand switches, particularly their involvement in decision-making and willingness to pay for choice of medicine brand.

Methods

A series of natural experiments was conducted to meet the first objective (Part 1), using centralised government health datasets, and selecting patients using lamotrigine, olanzapine, risperidone or venlafaxine as the study medicines. Outcomes measures included use of emergency services, hospitalisations and referrals to specialist services, as well as rates of deaths
and reports to the national adverse reactions centre. Data were retrieved from the national datasets for periods before and after each intervention, for both a study group and a comparator group, and difference-in-differences comparisons were made.

To determine the patients’ perspective (Part 2), a survey was conducted with the assistance of participating pharmacies throughout New Zealand.

**Findings**

No change in health services use was found following generic reference pricing, and hence no additional costs for heath service use could be attributed to the policy for any of the four medicines. However, low rates of substitution to the less expensive generic version were observed, and barriers to greater generic uptake were revealed.

The role of patients in deciding to switch brands appears to be minimal and their knowledge regarding the objectives of PHARMAC purchasing strategies appears weak.

**Conclusions**

Concerns regarding negative health impacts due to brand switching are not supported by the evidence presented in this thesis. Although generic reference pricing as applied in NZ is effective in containing costs, there is more that can be done to increase generic uptake and capitalise on financial gains, such as incentivising pharmacists and educating the public. Additionally, in the evaluation of purchasing policies, this thesis finds that using an epidemiological approach to mine national health datasets is feasible, although there are deficiencies in the data with respect to community-based services.

The findings presented in this thesis augment the international literature on generic medicines and reference pricing policies as well as the use of natural experiments in examining effects of health policies.
Acknowledgements

This thesis is a culmination of work contributed to by a collective to whom I am grateful: Professors Toni Ashton and Peter Davis provided expertise, guidance and enthusiasm; Joanna Stewart supported the statistical analysis of data kindly extracted by the NZHIS analysts; the many pharmacists and their patients who participated in the survey; Waimauku Village and Unichem Heather Moore pharmacies, and Waimauku and Silver Fern doctors who assisted with the pilot testing; the Health Systems Think Tank and anonymous reviewers who read and gave advice on journal articles; and input to the final version of this thesis from the examiners.
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## Abbreviations and acronyms

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<td>ACE inhibitor</td>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Classification</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BC</td>
<td>British Columbia (Canada)</td>
</tr>
<tr>
<td>CARM</td>
<td>Centre for Adverse Reactions Monitoring (New Zealand)</td>
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<tr>
<td>CDS</td>
<td>Chronic Disease Score</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>Cmax</td>
<td>Maximum plasma concentration</td>
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<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
</tr>
<tr>
<td>DHB</td>
<td>District Health Board</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (United States)</td>
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<tr>
<td>GDP</td>
<td>Gross domestic product</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>INN</td>
<td>International non-proprietary name</td>
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<tr>
<td>Medsafe</td>
<td>New Zealand Medicines and Medical Devices Safety Authority</td>
</tr>
<tr>
<td>MNZ</td>
<td>Medicines New Zealand</td>
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<tr>
<td>NHI</td>
<td>National Health Index</td>
</tr>
<tr>
<td>NICE</td>
<td>The National Institute for Health and Care Excellence (United Kingdom)</td>
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<tr>
<td>NMDS</td>
<td>National Minimum Dataset</td>
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<td>NNPAC</td>
<td>National Non-Admitted Patients Collection</td>
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<td>NZ</td>
<td>New Zealand</td>
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<tr>
<td>NZDep</td>
<td>New Zealand Index of Deprivation</td>
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<tr>
<td>NZHIS</td>
<td>New Zealand Health Information Service</td>
</tr>
<tr>
<td>NZPHD Act</td>
<td>New Zealand Public Health and Disability Act</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OPD</td>
<td>Out-patient Department</td>
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<tr>
<td>PBAC</td>
<td>Pharmaceutical Benefit Advisory Committee (Australia)</td>
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<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme (Australia)</td>
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<tr>
<td>PHARMAC</td>
<td>The Pharmaceutical Management Agency (New Zealand)</td>
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<td>PHARMS</td>
<td>The Pharmaceutical Collection</td>
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<tr>
<td>PHO</td>
<td>Primary Health Organisation</td>
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<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
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<tr>
<td>PTAC</td>
<td>The Pharmacology and Therapeutics Advisory Committee (New Zealand)</td>
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<td>Abbreviation</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>RMI</td>
<td>Research Medicines Industry (New Zealand)</td>
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<tr>
<td>SA</td>
<td>Special Authority</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
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<tr>
<td>Statin</td>
<td>HMG-CoA reductase inhibitor</td>
</tr>
<tr>
<td>STROBE</td>
<td>Strengthening the Reporting of Observational studies in Epidemiology</td>
</tr>
<tr>
<td>TG2</td>
<td>Therapeutic Group (2)</td>
</tr>
<tr>
<td>TPPA</td>
<td>Trans-Pacific Partnership Agreement</td>
</tr>
<tr>
<td>TRP</td>
<td>Therapeutic reference pricing</td>
</tr>
<tr>
<td>TV</td>
<td>Television</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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# Glossary

This list defines terms as used in this thesis, for clarity.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>bioequivalence</td>
<td>Bioequivalence is widely accepted as the marker of generic-for-brand interchangeability and can be defined as the absence of a significant difference in the rate and extent of absorption of the active ingredient that reaches systemic circulation</td>
</tr>
<tr>
<td>biopharmaceutical</td>
<td>Also ‘biologically-derived pharmaceuticals’ and ‘biological’. A pharmaceutical that has been manufactured in, extracted from, or semi-synthesized from a biological source. Different from a chemically synthesised pharmaceutical product, in degree of molecular complexity and isolation from human, animal, or microorganism source.</td>
</tr>
<tr>
<td>biosimilar</td>
<td>A biological medicinal product ‘similar’ to that of a patented biopharmaceutical product.</td>
</tr>
<tr>
<td>differential cost sharing</td>
<td>Where patients pay a prescription co-payment and that payment changes with price of the medication. The assumption which underpins differential cost sharing is that of interchangeability of all medicines within a category. Different systems exist including reference pricing, proportional cost-sharing and tiered systems. Fixed cost-sharing is represented by an absolute, unchanging co-payment.</td>
</tr>
<tr>
<td>enantiomer</td>
<td>Molecules that are mirror-images of one another, and which cannot be superimposed over each other.</td>
</tr>
<tr>
<td>generic</td>
<td>A generic medicine is a copy of an innovator medicine, marketed after the patent and period of exclusivity of the innovator (or originator) brand has expired. The generic name of a medicine is the non-proprietary name (INN) of the active ingredient in a pharmaceutical preparation. Generic drugs are marketed under a non-proprietary or approved name rather than a proprietary or brand name. For example: Generic name = Paracetamol Branded generic = Paracare® and Parapaed® Innovator (originator) brand = Panadol®</td>
</tr>
<tr>
<td>Innovator or originator</td>
<td>Term used to describe the on-patent version of a pharmaceutical preparation, i.e. the original brand of that medicine.</td>
</tr>
<tr>
<td>International Non-proprietary Name (INN)</td>
<td>An INN is the internationally recognised name of a pharmaceutical substance, a record of which is managed by the World Health Organization. It is the name of a medicine’s active substance, irrespective of the manufacturer or branding.¹</td>
</tr>
<tr>
<td>medicine-naive</td>
<td>A patient who has not previously received that medicine.</td>
</tr>
<tr>
<td>me-too</td>
<td>Pharmacologically similar medicines which have claims of therapeutic advantages over one another, and used for the same indication, but are chemically differentiated from other class members. The variant may offer better absorption giving it a better bioavailability and perhaps allowing a lower dose to be used, or it may exhibit less adverse effects for example.</td>
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| policy compliance | Schneeweiss (2001) differentiates ‘policy compliance’ to describe patients who consciously comply with the intention of the policy, from that of compliance as witnessed in clinical trials or drug therapy compliance. In this regard, policy non-compliance might be enacted by a patient continuing to take the higher priced, either by exemption or by paying out-of-pocket for it. A further action, policy avoidance is also possible, whereby a patient, and their prescriber doctor, substitute the policy affected medicine with a medicine from another, reimbursed, class.

This thesis uses the terms ‘switchers’ and ‘non-switchers’, rather than compliers and non-compliers, not to imply any degree of conscious action, but rather as an observation of those who have and have not switched. |
| switch-back | Changing from one brand to the previously used brand within 30 days (i.e. before the next monthly dispensing is due) |
Co-authorship forms

Co-Authorship Form

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Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

Nature of contribution by PhD candidate: Manuscript preparation, data collection and analysis

Extent of contribution by PhD candidate (%): 80%

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The undersigned hereby certify that:
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- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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Do users of risperidone who switch brands because of generic reference pricing fare better or worse than non-switchers? A New Zealand natural experiment. Accepted for publication in Administration and Policy in Mental Health. DOI 10.1007/s10488-014-0666-9. Content from this paper is included in Chapter 5 of this thesis.

| Nature of contribution by PhD candidate | Concept, data analysis and manuscript preparation |
| Extent of contribution by PhD candidate (%) | 80% |

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The impact on health outcome measures of switching to generic medicines consequent to reference-pricing: the case of olanzapine in New Zealand. Accepted for publication in Journal of Primary Health Care. Content from this paper is included in Chapter 5 of this thesis.

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## Certification by Co-Authors

The undersigned hereby certify that:
- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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An evaluation of health service impacts on switching to generic venlafaxine in New Zealand: the role of health professionals. Accepted for publication in Value for Health. Content from this paper is included in Chapter 5 of this thesis.

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New Zealand patients’ understanding of brand-substitution and opinions on co-payment options for choice of medicine brand. Submitted for publication in Australian Health Review. Content from this paper is included in Chapter 6 of this thesis.

Nature of contribution by PhD candidate: Concept, data analysis and manuscript preparation

Extent of contribution by PhD candidate (%): 80%

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Last updated: 25 March 2013
Chapter 1. Laying the foundation

1.1. Introduction

1.1.1. The pharmaceutical industry

Apothecaries prepared most medicines from plants and minerals until the late 19th century, when the chemical synthesis of medicines such as the barbiturates and the production and marketing of salicylic acid as ‘Aspirin’ moved pharmaceuticals from the periphery of disease management to centre stage. Demand for penicillin to meet war time needs in the 1940s was matched by technologies allowing large-scale production, and in the 1950s the discovery of haloperidol and chlorpromazine slowed the use of lobotomies and electroconvulsive shock therapy in patients with severe mental health disease.\(^2^,3\) The launch of zidovudine and other anti-retroviral medicines in the later part of the 20\(^{th}\) century for the treatment of human immune-deficiency viral infections changed the course of the potentially fatal disease to that of a manageable chronic illness, and the frontier of pharmaceutical research looks toward biologically-derived complex substances targeting specific receptor sites, and gene therapy. Pharmaceuticals are now firmly the mainstay of medical treatment, yet availability of these increasingly complex and costly preparations does not guarantee access to them. The pharmaceutical industry is undoubtedly a profitable market with worldwide revenue anticipated to reach a US$1 trillion in 2015\(^4\) and profit margins exceeding those of the lucrative banking and oil industries. Yet access to medicines remains problematic even in industrialised nations.

Countries of the Organisation for Economic Co-operation and Development (OECD) spent an average of 16% of health expenditure on medicines in 2011, although there was wide variability.\(^5\) Norway and Denmark spent the lowest at 7% of their total health expenditure on medicines, whilst Luxembourg, Netherlands and Switzerland were similar to New Zealand’s 9% spend. Some OECD countries such as Mexico and Hungary, however, spend up to 30% of their health budget on medicines.\(^6\) However, the rate of expenditure on pharmaceuticals is estimated to be increasing at around 5-6% per year, faster than on other aspects of healthcare and faster than increases in gross domestic product (GDP).\(^7\)

New Zealand, however, appears to be an exception to these escalating costs. Expenditure on pharmaceuticals has been maintained at a relatively constant rate of around 0.8% of GDP (approximately 0.84% in 2005 and 0.87% in 2010),\(^8\) whilst total expenditure on health as a percentage of GDP increased from 8.4% to 10.1% in the same period.\(^9\)
1.1.2. Managing the pharmaceutical budget: reference pricing

One of the primary strategies to maximise purchasing efficiency, employed by many countries including New Zealand, is reference pricing. Reference pricing establishes a single reference price for a group of drugs that are regarded as interchangeable. At the simplest level, ‘generic reference pricing’ groups medicines which have the same active ingredient (generic equivalents). ‘Therapeutic reference pricing’ considers those which are different chemical entities but are considered to be within the same therapeutic class (e.g. angiotensin-converting enzyme inhibitors), or those which are dissimilar but are used to treat the same conditions (e.g. analgesics). The reference price thus becomes the maximum reimbursable price for any drug within the defined category.10

Consequences of reference pricing manifest throughout the medicine supply chain - from producer to patient. Pharmaceutical companies can choose to re-price their products to match the reference price and thereby maintain their foothold in the local market, or to maintain the price difference at the risk of losing their market share. Reference pricing also exerts pressure on the prescriber, pharmacist and patient to choose either to switch to the referenced product or to use an alternative product with possible cost implications.

Generic reference pricing, which in essence is preferentially purchasing (or funding) generic medicines over their more expensive equivalent originator brands, offers potential savings of the order of up to 80% or even more,11 and in NZ considerable savings to the annual pharmaceutical budget have been made in preferentially funding generic medicines. For example, in 2010 expenditure on originator brand olanzapine was approximately NZ$30 million; by purchasing generic olanzapine at 4% of the price of the originator this amount has been reduced to less than NZ$10 million/year, even with increased usage.12 However, there are considerable inter-country differences both in price and in market penetration. Australian data indicates prices for generic medicines are on average 7-fold higher than the same generic medicines in England, and higher than that of the USA and NZ.13 Similarly, regional variation is evident in Canada, with prices for generic medicines in Ontario higher than British Columbia, as well as being higher than in NZ and the USA.14 Generic market penetration is also lower in some countries than others, for example total market share of generics in Belgium, Italy and Luxembourg was lower than in other EU countries in 2013 with less than 15% of prescribed drugs being generics.9,15 In this regard, NZ sits alongside that of Germany, the UK, Denmark and the Slovak Republic, at levels greater than 70%.9

Although it would appear that NZ maximises the advantage of purchasing generic medicines and thus makes savings to the annual expenditure, opponents of the practice argue that it delays the introduction of innovator products to the national formulary with consequent
health opportunity loss, suggesting that the NZ Pharmaceutical Management Agency (PHARMAC) waits for generic equivalent brands to become available before funding the medicine. Additional arguments against reference pricing policies include the position that it restricts the prescribing freedom of medical practitioners, increases inequity in the health sector (as only those who can afford to pay for non-reference priced drugs can access them), has negative clinical consequences and increases the use of other health services.

Further resistance to the substitution of originator brand medicines for their generic counterparts centres on the issue of bioequivalence. Bioequivalence is widely accepted as the marker of generic-for-brand interchangeability and is regarded as the absence of a significant difference between generic and comparator in the rate and extent of absorption of the active ingredient that reaches systemic circulation. A limited number of medicines have been traditionally considered non-interchangeable, either where bioequivalence has not been established or where the risk of toxicity is high. Examples of such medicines include warfarin, digoxin and phenytoin. Despite this, successful substitution with generic cyclosporine, long considered the archetypical non-interchangeable medicine, has been reported in heart transplant patients.

Bioequivalence studies are, however, generally conducted in small numbers of healthy volunteers, leaving the studies open to criticism. The conduct of randomised and blinded clinical trials as the accepted standard used to evaluate efficacy of one medicine over another is expensive (especially given that generic manufacturers do not have the resources of the large multinational companies), and seem logically unnecessary to confirm a generic’s clinical equivalence when the required standard of bioequivalence has been established. Establishing bioequivalence, however, does not guarantee acceptance of the 'same-but-different' generic medicine by health professionals or patients, and concerns linger around the interchangeability of generic medicines with their originator counterparts. Blurring the evidence base on bioequivalence is the existence of journal publications using inadequate study designs, many of which are privately funded or are possibly limited in the extent of their peer-review processes.

Evaluations of reference pricing policies, which utilise natural experiments and well-designed observational studies can fill this evidence void, yet are limited, with most studies evaluating market share and prices of the referenced products and few measuring patient-centred outcomes. The majority of studies evaluating clinical outcomes originate from British Columbia in Canada, and are conducted amongst the elderly. In general, these studies found no evidence of increased health service use, except for a transient increase in visits to the doctor, and no evidence of increased mortality amongst patients subject to policies of reference pricing. Concern over the potential for reimbursement policies to increase rates of
discontinuation of therapy for certain classes of medicines such as the antipsychotics have been expressed.\textsuperscript{34}

As clinicians, Al Ameri and colleagues, in questioning the ethics of substitution, suggest that medicine “ought to have no other role than taking care of the interests of patients” (Al Ameri, 2011:881).\textsuperscript{35} They argue that if there are insufficient resources, additional funding must be made available rather than turn to policies of reference pricing and cost minimisation.\textsuperscript{35,36} In response, from the population health perspective, Simoens holds that “it may be ethical to substitute the reference with a generic medicine even if the generic medicine is less effective than the reference medicine” (Simoens, 2001:469).\textsuperscript{37} In doing so, Simoens advocates for a societal perspective which considers that the potential benefit to a population’s health in making resources available through purchasing less expensive technologies, offsets any reduction in clinical outcomes of an individual or specific patient group.

This is the fundamental predicament faced by national healthcare providers and insurers: balancing access to the most effective, often expensive medicines whilst containing total pharmaceutical expenditure; meeting the health needs of the individual, yet not at the expense of society.

With a wealth of experience in managing pharmaceutical expenditure over the past 20 years, the New Zealand experience with reference pricing offers insight into this dilemma.

1.1.3. New Zealand’s experience

New Zealand operates a publicly-funded healthcare system, which accounts for the majority (80%) of total health expenditure, including the provision of medicines. New Zealanders receive publicly funded prescription medicines for items listed in the national formulary, the ‘Pharmaceutical Schedule’, with a co-payment per prescription item required.\textsuperscript{38,39} Medicines not listed in the Schedule are not funded, with patients having to bear the full cost. The Pharmaceutical Management Agency of New Zealand (PHARMAC), a managerially independent Crown agent answerable to the Minister of Health, is responsible for the management of the Schedule and access to medicines.

PHARMAC operates in similar ways to its sister agencies, the Pharmaceutical Benefits Advisory Committee (PBAC) in neighbouring Australia and the National Institute for Health and Care Excellence (NICE) in the UK, in using pharmacoeconomic and technology appraisal techniques to make funding decisions, and also draws on the experiences of pharmacy benefits agencies in the USA, Canada, Germany and the wider international community.
PHARMAC, in collaboration with the District Health Boards, sets the fixed annual budget and as charged, has managed to maintain expenditure on community pharmaceuticals within successive annual allocations, to the approbation of similar agencies in other countries. Using a combination of purchasing policies PHARMAC estimates that it has saved more than NZ$1 billion from the budget in the 10 years from 2000 to mid-2011, and off-patent tendering policies alone has saved NZ$600 million since 1997. Whilst consistently being one of the few departments to stay within budget, PHARMAC has enjoyed the support of both a Labour-led government for many years as well as the current National-led government, and has stood the test of time. Not only has PHARMAC continued to exist where structural changes have been implemented in the sector, but in 2012 was given an expanded role by the government in the procurement of hospital medical devices and vaccines.

Independent scrutiny of the operations and impact of PHARMAC overall has, however, been limited to one formal review, to judicial reviews of specific funding decisions, ‘ad-hoc’ challenges by consumers, doctors and the pharmaceutical industry, which often play out through the media, and limited university-funded studies. The NZ public have been exposed to the PHARMAC model of medicines management since the mid-1990s, yet resistance to PHARMAC policies persists, and pressure may be mounting from other sectors. PHARMAC pricing policies are seen as discriminatory by multinational pharmaceutical companies, and US trade discussions seek to influence both PHARMAC and Australia’s Pharmaceutical Benefit Scheme. Current drug developments which promise the advent of biopharmaceuticals are certainly destined to be expensive, making their inclusion in formularies a challenge to funders. Adalimumab injection used in rheumatoid arthritis, for example, in 2015 costs NZ$1,800/person/month, yet at least five biosimilar equivalents are soon to be launched, making the medicine potentially less expensive and more accessible.

PHARMAC policies have been described as “aggressive” and although many laud the achievements of the agency, not all are advocates. Key opinion leaders are not all in accord in their influence over acceptance by patients of reference pricing and other practices, and are thus open to leverage by the pharmaceutical industry. A formal generic policy does not exist in New Zealand and generic medicines are still viewed with distrust, making the acceptance of biosimilar medicines in the new era of biopharmaceuticals doubtful, and the gains that PHARMAC has made over the years under threat.

Yet the opportunity exists to provide evidence for the effect of reference pricing on clinical outcomes, and provide a sound base for pharmaceutical funding decision-making. Methodologies for conducting well-designed observational studies are established, and a
wealth of electronic health information including pharmaceutical data is collected in New Zealand to support such studies.

1.2. This thesis

New Zealand patients enjoy access to medicines above that experienced by patients in many similar nations, largely due to the policies of PHARMAC. However, tensions exist at the periphery: access to new, expensive pharmaceuticals including biologically-derived medicines, medicines for rare conditions, or those with marginal proven benefit over existing therapies, must be balanced with the available resources to fund their delivery. PHARMAC at times must make ‘tough decisions’ and account for these decisions to patients, who at times are fearful of and resistant to change, and they do so in the absence of consolidated support from the medical fraternity and in direct opposition to the financial desires of the pharmaceutical industry.

When a new medicine is brought to PHARMAC for consideration for funding, a decision-making process is triggered which includes both an examination of effectiveness of the new medicine and of its cost against similar therapies. In essence this is reference pricing: examining the cost-effectiveness of one medicine against others. PHARMAC may decide to preferentially award full access to this new medicine over others, triggering a formulary change. In turn, this necessitates that patients also give preference to the new medicine and change to using it, or pay for using the alternative.

At the least complex level of such formulary decision, lies generic reference pricing – the preference of one brand of a particular medicine over another. More complex comparisons between different medicines are also made by PHARMAC and similar agencies in determining which preparations to fund. The reason to reference medicines against one another remains the same – cost-effectiveness; however, the reasons put forward against reference pricing become increasing more complex as the diversity of comparisons increase.

Examining PHARMAC’s policy of generic reference pricing and the effects of policy compliance and non-compliance, as a series of natural experiments is both feasible and needed. There will always be generic versions of patented medicines coming to market, and judicious spending of the available resources by PHARMAC will mean continual changes in the preferred, funded brand. A process of generic reference pricing that has been examined, with any weaknesses exposed and put right, that can be endorsed wholeheartedly by opinion-leading clinicians and the public, is essential to a smooth functioning system. Generic reference pricing should not be part of the ‘tough decisions’ that PHARMAC or patients have to make and this thesis endeavours to augment the international knowledge base informing such decisions.
1.2.1. Research question

Do New Zealand patients who switch brands because of generic reference pricing fare worse than non-switchers?

1.2.2. Aim of this thesis

This thesis takes advantage of nation-wide policy interventions of generic reference-pricing to evaluate the clinical and economic outcomes of patients affected by such interventions. It aims to enumerate any change in outcomes consequent to policy-driven changes for specific exemplar medicines in the Schedule, and to explore the motivations of patients in choosing to switch (or not) between medicine brands, as well as their willingness to pay for an alternative unsubsidised medicine.

1.2.3. Specific study objectives:

For certain exemplary medicines against which PHARMAC has implemented generic reference pricing, to:

- describe the effect of the policy on patients’ patterns of medicine usage
- evaluate the effect on health outcomes (morbidity and mortality) of switching from the originator brand to a generic equivalent
- determine any consequent change in associated health services utilisation and costs.

And, to understand the patients’ perspective on switching between medicines, including:

- describing the attributes of patients who continue to use the originator brand of a specific medicine (‘non-switchers’) from those who switch to using a generic equivalent (‘switchers’)
- understanding their reasoning for switching or not
- describing additional or hidden costs borne by the patients in switching or not
- evaluating willingness to pay for an alternative choice.

1.2.4. Hypotheses

The hypotheses that underpin this thesis are that:

- no adverse health outcomes result from switching brands of the exemplar medicines
- measurable demographic attributes of patients can be used to predict the likelihood of patients to switch brands
• the cost of any difference in health service utilisation between ‘non-switcher’ patients and ‘switchers’ is offset by the economic benefit of reference pricing
• despite certain limitations, the New Zealand health datasets can be used to evaluate the impact of reference-pricing, and provide evidence which can be used to guide further pricing policy-making.

1.2.5. Thesis structure
This chapter lays the foundations for the studies contained within this thesis. It describes the dilemma faced by health funders in delivering quality pharmaceutical care whilst containing overall expenditure. Chapter 2 further elaborates on management strategies to contain pharmaceutical consumption and expenditure and provides a review of the available evidence on reference pricing and generic substitution. Chapter 3 describes the NZ setting and the specific strategies employed especially by PHARMAC in the context of delivery of affordable pharmaceutical care.

This study can be viewed as a two-part, two-method study each part complementing the other, with Chapter 4 describing the methodology employed in the first set of research objectives (Part 1), including the rationale for selection of the four exemplar study medicines. Chapter 5 presents the findings for the individual medicines, all of which have been published in peer-reviewed journals, the details of which are given at the start of each case study. Part 2 is presented in Chapter 6, which describes the questionnaire-based study conducted to meet the second set of objectives from the patients’ viewpoint. Much of the content in chapter 6 has also been submitted for publication.

The implications of the findings from the four exemplar medicines’ studies are discussed in Chapter 7 together with findings from the patient survey, before recommendations and concluding remarks are made in the closing chapters.

1.2.6. Ethics approval & Research funding
This study was approved by the University of Auckland Human Ethics committee and permission to access patient data was received from the Ministry of Health of New Zealand. Approval for data extractions was obtained on 23rd August 2012 (Ref. 8180), and for the survey on the 26th November 2012 (Ref. 8776).

University of Auckland Postgraduate Research Student Support (PReSS) Funds, only, were used to conduct this research. I have been the recipient of a University of Auckland Senior Health Research Scholarship and have received no other financial support. I have no conflict of interests to declare.
Chapter 2. Pharmaceutical expenditure

This chapter gives an overview of strategies and purchasing policies used to minimise pharmaceutical expenditure, additionally considering managerial approaches such as those directed at prescribers and patients. A focus on reference pricing, as a primary cost-minimising strategy, is then made, drawing on interventions described in the wider literature; the effects of reference-pricing policies are described and gaps in the knowledge base highlighted.

2.1. Introduction

Expenditure on pharmaceuticals varies widely amongst countries of the OECD, both in total expenditure as well as per capita, yet there is no agreement on the ‘right’ amount to spend. In 2005 the OECD average annual per capita expenditure on pharmaceuticals was US$400, with the USA spending US$800 at one extreme and New Zealand spending US$300 per capita per annum at the lower end of the spectrum. Notably, the USA hosts many of the largest international pharmaceutical companies and accounts for almost half of global sales. New Zealand, in contrast, has only a few, small manufacturing companies producing mostly generic medicines. By 2012 spending in the USA increased to more than US$1000 per capita, with a similar trend apparent in many countries, including neighbouring Australia. During the same periods, however, New Zealand held pharmaceutical expenditure constant (at around US$300 per capita per year).

2.2. Management strategies to minimise expenditure on medicines

Pharmaceuticals, being complex chemicals used in complex health conditions, are not simple commodities purchased by citizens. Instead, doctors and other health professionals act as ‘agents’ on the patient’s behalf in much of the decision-making process. In this regard, price sensitivity of medicines is low – patients will continue to purchase medicines even as the price rises - especially where insurance coverage is in place, except at the extremes of high price or low income when patients might defer collecting their prescribed medicines.

This price inelasticity benefits producers of innovator medicines, where competition by generic equivalents is prevented for the duration of a patent. Manufacturers will attempt to bring the new medicine to the market at the highest possible price, arguing that both the high price and exclusivity period are necessary consequences of the associated research and development costs. In turn this moves the decision whether to provide access to the new medicine onto funders. Pharmacoeconomic principles as applied by PHARMAC, NICE, the PBAC and similar agencies, using evidence-based technology assessments and cost-effectiveness analyses, provide the mainstay for funding decisions, (although even in the absence of clear
evidence of clinical effectiveness, funding of certain medicines does occur\textsuperscript{47}). Once the decision has been made that a medicine would be a valuable inclusion in the formulary, funders will use a variety of pricing strategies to achieve an acceptable cost burden for its usage, either by limiting the volume consumed or the reimbursable price of the medicine.

2.2.1. Strategies to limit consumption

\textit{Influencing the prescriber}

Efforts directed towards limiting consumption can be focused on prescribers via several mechanisms, and the adoption of different mechanisms varies across countries\textsuperscript{75}. Whilst some countries rely on the medical profession taking responsibility themselves, others adopt more proactive centralised policies such as the use of formularies which may have restrictions embedded in them. Germany operates a ‘negative list’ containing preparations which, if prescribed, cannot benefit from the statutory health insurance\textsuperscript{76}, whilst many other countries use a positive list with various mechanisms for the listing of a preparation, including the use of a therapeutics committee to make assessments. Restricting the conditions for which a medicine will be funded or restricting the level of prescriber expertise, i.e. formulary restrictions, is one further step in influencing prescribing behaviour, a mechanism used in NZ (Special Authority conditions are described in the next chapter of this thesis, Chapter 3). Providing educational activities and incentives, as well as setting prescribing targets with feedback are also methods used to influence prescribing habits; however, an assessment of the influence of such activities suggests the effects are limited when conducted in isolation of other policies\textsuperscript{75,76}.

Capping the practice- or prescriber’s-budget is yet another feature of some OECD country’s policies including the UK, Germany and the Slovak Republic, with penalties imposed if the budget is exceeded. The effectiveness of capping budgets at this level is mixed however, with effect on the quality of care questioned, and resistance amongst physicians reported\textsuperscript{77,78}.

\textit{Influencing the patient}

Cost-sharing as a policy tool is used to influence patient demand for medicines on the basis that if a patient shares a portion of the cost they are likely only to purchase (or demand) a medicine when they deem it necessary. Indirectly also, awareness by prescribers of the extent of co-payments may influence prescribing behaviour. Fixed co-payments per prescription item are used in NZ with a safety-net of a maximum annual amount; however even this has been found to adversely affect access to medicines, especially amongst indigenous Māori and Pacific peoples, with 7% of patients deferring collecting a prescription due to cost\textsuperscript{79,80}. Australian patients, similarly pay a fixed co-payment amount set by the PBAC, (unless the cost of the medicine is less,
in which case this amount becomes payable) and safety nets also exist. Tiered co-payments are commonly used in private insurance schemes where a higher co-payment is required for choosing a non-preferred item.

Cost-sharing policies do reduce overall medicine use and expenditure; however, undesirable effects occur such as reductions in the use of essential medicines, especially those used in chronic illnesses, with the potential for costs to be shifted to other sectors of the health system.81 A Cochrane review of studies on the effect of reimbursement restrictions included 29 studies, mostly involving older patients or low-income populations and found the impact of restrictions was dependent on the class of medicines affected. Targeting the (over)use of gastric acid suppressant, antihypertensive medicines and statins for example, resulted in decreased use and overall savings, whilst an adverse impact (increased use of other health services) was found when antipsychotic medicines were targeted.84

Patient choice is the basis for a reference-price reimbursement policy. In this policy, the insurer/funder determines the maximum reimbursement price for a cluster of similar medicines, with the patient exerting their preference and paying any cost-difference for that choice. In the US the use of tiered formularies is common, mostly structured with 3 tiers – generic medicines, products which have an agreed rebate, and non-rebated products – with the patient paying an incrementally higher co-payment to exert their choice.82 Tiered formularies are thus similar in intent to reference pricing, such as applied in New Zealand’s Schedule, in the circumstance where a branded medicine remains listed but with a co-payment required from patients.

**Influencing the pharmacist**

In the context of formulary funded medicines, the pharmacist’s role in limiting consumption is less obvious as it is generally their role to ensure consumption of the medicine as prescribed. It might be in preventing wastage that the pharmacist limits an individual’s consumption, yet a more likely role is in the preferential choice between two brands of the same medicine with different prices. Pharmacists are well placed to increase overall consumption of less expensive generic medicines over more expensive brands, and to provide information on generics to patients and prescribers in this regard, yet they may need to be incentivised to take up this role.75,83 In Australia, for example, other than competition amongst pharmacies, no incentive exists to provide the least expensive brand other than that below the maximum patient co-payment level.84
2.2.2. Strategies to lower the price

The players involved in setting prices of medicines include the supplier, any competitors, the purchaser (or insurer or funder) and any outside influence (e.g. political, strategic, or existence of an over-arching policy). Suppliers seek to maximise the price and market share, whilst the purchaser attempts to minimise costs.

One of the major pricing strategies used by funders is reference pricing which, very simply, describes a policy of comparing prices for a given product before setting the level of reimbursement which will be paid for it. As manufacturers and suppliers are free to set their market prices above the reference price, reference pricing is not considered an explicit price control method,\(^{32,67,69,85}\) however, as patients are often expected to pay the price difference, indirect pressure is exerted on pharmaceutical companies to compete by reducing prices or risk losing market share. Tiered co-payments, in addition to steering patients towards using more cost-effective options with a treatment category, and thus reduce expenditure by the funder or insurer, also serve to influence the manufacturer’s price in return for listing as the preferred tier in a formulary.\(^82\) Similarly, in NZ reference pricing is commonly used to determine inclusion of a product in the Schedule, with the possibility of a sole-supply contract for the supplier and as such it is a more explicit pricing policy.

Reference pricing often sits alongside other pricing policies such as negotiated prices, competitive tendering, maximum fixed prices, price-volume controls, parallel importation and price cuts or freezes,\(^69\) however, the focus of this thesis centres on generic reference pricing, and the remainder of this chapter will concentrate on a review of the literature on reference pricing.

2.3. Reference Pricing

2.3.1. A typology for the clustering within reference pricing

Different methods of clustering of the medicines to be included in a reference group give rise to a different nomenclature in the literature. ‘External reference pricing’ refers to when the reference price has been derived from prices of the same medicine in a cluster of reference countries (i.e. international price comparison),\(^69\) and similarly ‘internal reference pricing’ refers to comparison of clusters of therapeutically similar medicines within a single country. External reference pricing is also termed ‘benchmark pricing’ and the terms ‘exogenous’ and ‘endogenous’ reference pricing have also been described.\(^86\) ‘Index pricing’ has been used to describe a dynamic form of reference pricing which is reset periodically by a described formula as prices change over time.\(^87\)
Internal reference pricing is further divided by the extent to which medicines are considered therapeutically similar. Most commonly, the World Health Organization’s Anatomical Therapeutic Chemical (ATC) Classification System (ATC) classification is used as a basis, dividing medicines into groups according to which organ or system they affect, and with 5 levels of increasingly more specific subgroups. The 5th ATC level describes the exact chemical entity of a preparation (also called the International Non-proprietary Name or generic name) and at this level, medicines containing the same active substance are considered equal. Internal reference pricing at this ATC level is termed ‘generic reference pricing’.

When clusters of medicines at the 3rd and 4th ATC levels are used to set a reference price, the term ‘therapeutic reference pricing’ is conventionally used. Therapeutic reference groups might include medicines which are slightly different chemical entities with comparable pharmacological indications (e.g. the group of angiotensin-converting enzyme inhibitors may be clustered in a single ATC level 4 reference group), or the grouping might be extended to include all medicines which are used to treat a particular (ATC level 3) condition (e.g. high blood cholesterol, whereby the HMG-CoA reductase inhibitors [“statins”] might be reference priced alongside fibrates and nicotinic acid derivatives). The level 4 ATC class contains pharmacologically similar medicines which have claims of therapeutic advantages over one another (often called “me-too” medicines). Such medicines are used for the same indication, but are chemically differentiated from other class members. The variant may offer better absorption giving it a better bioavailability and perhaps allowing a lower dose to be used, or it may exhibit less adverse effects, for example. It is this inter-class similarity that is exploited when therapeutic reference pricing is applied to a class of medicines, and it is on this basis that pharmaceutical companies argue their individual point of difference. For example, Pfizer argued that its product atorvastatin held significant clinical advantages over the other statins, and managed to have it excluded from therapeutic reference pricing in many countries, exceptions being Germany and Hungary. The basis on which groups are clustered and considered clinically interchangeable at ATC level 3 can be even more contentious, such as the inclusion by the Netherlands of the newer group of triptans for the management of migraine headaches in the same group as the older ergotamine derivatives.

Where the WHO ATC classification system is not used, such as in the USA, other methods of categorisation are applied. In the USA, for example, RxNorm is a vocabulary maintained by the National Library of Medicine for naming medicines.

Setting the reference price

Depending on a country’s adjunctive policies the reference price of a cluster of medicines may itself be set in a number of ways. Principally, if the objective is simply to achieve the lowest
price, then the reference price against which all in the cluster will be measured is the lowest price amongst the group. Variations on the lowest price approach exist, such as using the mean price of the cluster, or giving proportional advantage to generics over their originator counterpart. In the late 1990s, the Netherlands calculated the price per defined daily dose (DDD) for originator and generic products for each medicine, and set the reference price at the median point. Similarly, Spain for example, used the lowest three prices per DDD in a cluster to set the reference price of statins once generic versions were available. Other computations of a reference price will attempt to incorporate policies which stimulate local pharmaceutical production, or give recognition to international treaties.

2.3.2. International experience with reference pricing

*External Reference Pricing*

External reference pricing, or benchmarking, is commonly employed amongst member states of the EU (20 of 27 members) and OECD (24 out of 30). The exact implementation varies across countries, with some applying it to only on-patent medicines, and some (more commonly developing countries) applying benchmarking to both on- and off-patent products.

Aside from one study in Norway which reported a small reduction in price consequent to benchmarking, few validated studies exist to provide evidence of reduction in price of medicines obtained using this strategy. Some evidence exists of market manipulation whereby suppliers use benchmarking to advantage. For example, prices in Germany are used as an external reference source for other countries such as Holland and Italy, and in this case it is potentially more advantageous to hold a somewhat higher price in Germany and risk losing market share, for the gains to be made in the other countries. Examples of this practice have been noted for calcium channel blockers and atorvastatin in Germany, as well as for simvastatin in NZ, and angiotensin-converting enzyme inhibitors (“ACE inhibitors”) in one province of Canada. Confidential agreements between the insurer and manufacturer are commonplace, leaving the publicised price higher than the delivered price, aiding a higher benchmark price. Using more than a single comparator and instead setting a price at the median of a number of prices for different products can minimise this effect, as can index pricing, whereby the reference price is periodically reset as international prices change.

*Generic reference pricing*

Generic policies, which include generic procurement, prescribing and dispensing (generic substitution) have been well established in many developing nations from at least as early as
1972 in Pakistan. In 1989, faced with rising healthcare budgets, Germany initiated a series of healthcare reforms including generic reference pricing and several European countries followed thereafter. Generic reference pricing is now employed by at least 22 countries in the European Union, as well as in Australia, Canada, and New Zealand. In addition, reimbursement based on a maximum allowable charge for generic equivalents has long been established in state Medicaid and other managed care programs in the United States.

**Bioequivalence of generic medicines**

To be registered for use, a generic medicine must demonstrate that both its overall bioavailability and maximum plasma concentration are within the 80–125 % confidence limits of that of the originator brand. This is a requirement of most regulatory agencies including the United States Food and Drug Administration. In reality however, the variations are much lower. A review of 2070 submissions to the FDA for generic products found that 98 % of all bioequivalence studies showing a variation of less than 10 % with little variance in the bioavailability (3.6 %; SD = 2.9) and maximum plasma concentration (4.4 %; SD = 3.5). If bioequivalence has been established then the originator brand can be substituted with the generic equivalent version, and can be relied on to achieve similar clinical results and safety profile.

A limited number of medicines are traditionally considered ‘non-interchangeable’, where the therapeutic index (range between effective plasma concentration and toxic level) is narrow and the risk of toxicity is high (older anti-epileptic medicines and digoxin for example). Despite this, successful substitution with generic cyclosporine, long considered the archetypical non-interchangeable medicine, has now been reported in heart and renal transplant patients.

Establishing bioequivalence, however, does not guarantee acceptance of the ‘same-but-different’ generic medicine by health professionals or patients, and concerns linger around the interchangeability of generic medicines with their originator counterparts. The American Academy of Neurology 2006 guideline (still in force) for example, opposes generic substitution of all anti-epileptic medicines without physician approval, as does the American Psychiatric Association with regard to psychoactive medicines. Misinformation and suspicion is commonplace amongst pharmacists and doctors on the bioequivalence and hence on the substitutability of generic products, and influences the attitudes of patients. Whilst pharmacists in Sweden and some doctors in the US agree that generics are better value for money, other US and Ireland doctors report they would rather not use generics themselves. Health professionals in Sweden, Ireland, Finland, and Italy feel that changing medicine brands creates confusion amongst patients. Multinational pharmaceutical companies are active in resisting generic market penetration for obvious reason
and, uniquely in New Zealand and the USA, are legally able to market their products and opinions on generic medicines directly to consumers.\textsuperscript{51,106}

**Therapeutic reference pricing**

Experience with therapeutic reference pricing is more limited. Six countries internationally, including New Zealand, have employed therapeutic reference pricing on classes of medicines such as HMG-CoA reductase inhibitors (the “statins”), ACE inhibitors and calcium channel antagonists. These ATC level 4 therapeutic classes contain medicines with claims of therapeutic advantages over one another (“me-too” medicines). Even fewer countries have used reference clusters based on a disease or condition, (i.e. Level 3 ATC grouping), as the cluster is less homogenous and prescriber resistance higher, and other incentives for preferential prescribing of one or more members of a reference cluster are more likely to be leveraged.\textsuperscript{10} The Netherlands clustered sumatriptan alongside older ergotamine products in a grouping of migraine treatments, for example.\textsuperscript{87} Countries which use therapeutic reference pricing rely on evidence-based technology assessments to argue the case for substitutability and hence inclusion in a reference group.

**NZ reference pricing**

NZ has applied therapeutic reference pricing to various groupings of statins since 1997, initially subsidising fluvastatin and reference pricing all available statins to it.\textsuperscript{107} In 1998 PHARMAC reference priced the therapeutic cluster of ACE inhibitors,\textsuperscript{108} and in the following year applied it to calcium channel blockers with members of the cluster referenced against the negotiated price of felodipine.\textsuperscript{53}

Therapeutic reference pricing in NZ has been described as the “most vigorously pursued” (Willison, 2001) in a study of seven countries using the pricing method (including five European countries and Australia and Canada). This is because within a therapeutic cluster, PHARMAC may consider novel originator medicines, “me-too” and generic products alongside one another, with the lowest priced in the cluster setting the reference price.\textsuperscript{109} In contrast, and in response to claims of patent infringements, Australia and Germany have effectively removed patented medicines from therapeutic reference pricing, limiting price comparisons to external benchmarking or direct negotiation.\textsuperscript{84,109}

2.3.3. Effect of reference pricing

Several reviews evaluating the effect of reference pricing have been published.\textsuperscript{10,31,32,87,90,100,111} Consensus regarding the quality of methodologies employed within
individual studies is equivocal, with some studies being excluded in one review, yet included in another. Aside from the reviews, there are several studies in the literature with inadequate study designs and others with the potential for a high degree of bias having been funded by the pharmaceutical industry itself.29,112-122

**Effect on Medicine Prices**

With the majority of OECD and European countries, the US and most developing nations using generic reference pricing, it is self-evident that there are gains to be made in purchasing generics. Price differentials (between generics and the innovator brand) of 40-50% have been reported for Canada, and up to 60% in the USA and 80% in the UK.10,14,111 Exceptions exist however, such as in Belgium,15,123 and Hungary where generic prices were only slightly lower than their innovator brand counterparts.118

Studies have found reductions in innovator brand price of 17% in Norway and 19% in Sweden10,124 and 27% in Germany consequent to reference pricing.125 Belgium reference priced lisinopril in 2002 with the emergence of generic versions onto the market. The brand product, which dropped its price to the reference price, increased its market share by 15%, whilst consumption of another branded product which held its price above the reference price decreased by 43% over the same period.123

However, entrance of competitor generics into the market does not necessarily drive the innovator brand price downward, possibly related to a company’s decision to focus on the market share of less price-sensitive consumers and on external reference pricing practices.125,126 Evidence of the latter has been documented in New Zealand and Germany whereby the price of certain products was held high in those countries despite local reference prices being lowered, since the companies knew they were used as a reference point for other countries setting internal prices and would rather attempt to gain a higher price in potentially larger markets.33,91

Evidence of collusion exists whereby generic companies game amongst themselves for market share and price. Finland and Australia report on paying higher prices for generics than comparator countries.84,127 Companies prefer to compete amongst themselves by offering discounts to pharmacy purchasers and leave the reference price unchallenged, such as has been found in the Netherlands and Spain.67,111,128 Furthermore, examples exist where prices increased (price convergence) to meet the reference price where it has been set higher than existing market prices, such as is the experience in the Netherlands and Spain.10,86,87

Unless some form of price regulation is implemented alongside reference pricing, no incentive exists for suppliers to reduce prices to any point below the reference price.87,129 Some countries implement price control measures where each successive company wanting their
generic product to be funded must price their product proportionately lower than the existing reference price (and thereby reset the reference price to a new, lower level). In Germany, the reference price is set higher where there are fewer generic products in the market in order to stimulate entry of generics into that group. This, combined with other policies such as price caps, is reviewed annually and a new, lower reference price set.37

The case for therapeutic reference pricing is less clear as fewer countries have experience with it.31 In Denmark, decreases in the list price (27%) and average co-payments (7.5%) were experienced following reference pricing of lipid modifying agents in 2005.130

Effect on Medicines Use

Few studies measure the impact of reference pricing policies on medicine use at an individual level, with changes in drug use mostly reported as aggregated data on market share. A general trend in decreased consumption of the non-reference priced product and increased use of the reference product has been found.

A Cochrane review of studies up to 2005 found 5 studies reporting an increase in dispensed reference priced drugs of 60%-196% immediately after the introduction of reference pricing, and a decrease in the use of cost-sharing medicines of 19%-42% in 4 studies.31

A review of studies conducted in British Columbia found overall 10%-50% of users switch to the alternative less-costly drug, with a slight reduction in dispensed daily doses.92 Furthermore, no increase in the rate of discontinuation or in substitution with more costly medications has been observed; however, an exemption system used by 10%-40% of patients may have affected the results.92

In Germany, following the reference pricing of statins, the manufacturer held the price of atorvastatin above the reference price and a volume shift to simvastatin subsequently occurred as the policy intended, with atorvastatin losing its market share from 33.3% down to 4.8% in 2006.131 However, Hungary also implemented therapeutic reference pricing of statins, with a reimbursement mechanism based on defined daily dosages (DDD). The average daily dose of statins per prescription however, increased from 1.14 to 1.65 as patients and doctors manipulated the system by splitting the higher strength tablets to receive the same reimbursements (lower co-payment) as before the reference pricing system was implemented.118

In British Columbia all histamine-2 receptor antagonists were reference priced against cimetidine, and special authority restrictions placed on PPIs resulting in a decrease in the total number of H2 antagonist prescriptions as well as initially for omeprazole.20 Later, consumption of omeprazole increased.10
Increased usage of the reference priced medicine can only be anticipated if disincentives to use non-referenced products exist, preventing a shift to medicines not included in the reference cluster. Evidence of re-allocation of demand exists. When Spain applied generic reference pricing to off-patent lovastatin and simvastatin, the policy did not include fluvastatin or atorvastatin, as their patents were still in force. An increase in consumption of these two non-referenced medicines was observed, ascribed to a lack of cost-consciousness amongst prescribers and patients and activity by the industry in favour of branded medicines. Similarly, Spain’s selective serotonin reuptake inhibitor cluster did not include venlafaxine and escitalopram and consumption of the latter two products increased whilst the anticipated increase in consumption of citalopram was not achieved.

Italy implemented generic reference pricing of the H₂ antagonists, with the manufacturers of ranitidine holding their price above the reference point. Consequently, the market share of ranitidine decreased, but an increase in market share of the generics was not evident, and instead an increase in the use of non-reference priced omeprazole resulted.

A study in the Netherlands reported on the use of proton pump inhibitors (PPI) following the expiry of the patent on omeprazole, with multiple generic versions of omeprazole entering the market. A downward trend in consumption of omeprazole was observed, with more patients switching to alternative PPIs pantoprazole and esomeprazole (an enantiomer) promoted by the manufacturers. A similar effect for omeprazole and esomeprazole was found in Belgium.

**Effect on Pharmaceutical Expenditure**

Depending on the medicines included in the reference cluster, moderate to large savings are potentially achievable, with savings largest where the price of the more frequently used medicine is substantially above the average of its competitor prior to referencing. Gains in the short-term of the order of 2% in Belgium, 5% in Italy, 1.5% in Denmark have been reported, but with no impact reported by Hungary or Spain and no established pattern of decreased expenditure after 6 months. One of the issues related to the effect of reference pricing on overall expenditure is the link between price and volume. Addition of a new medicine into a reference cluster might force the new entrant to lower the reference price for the cluster, but that increased consumption may, over time, counteract any gain in price reduction, and that expenditure overall may indeed increase.

Canadian studies on reference pricing of ACE inhibitors found a decrease in expenditure on anti-hypertensive medicines of 19%, and further a decrease of 12% was attributed to reference pricing of calcium channel blockers. In addition, there was less out-of-pocket expenditure for ACE inhibitors. The data showed declines in annual expenditures for drugs...
within three referenced clusters from $42.0 million the year before reference-based pricing was introduced, to $23.7 million the year after.\textsuperscript{92}

Norway adopted reference pricing in 1993, but due to insufficient cost-savings later abandoned it for other strategies including index pricing.\textsuperscript{10} A reduction in the price of some medicines was achieved however, together with a 13-15\% reduction in the level of co-payments.\textsuperscript{86}

Where reallocation of demand occurs, or some other unintended consequence of reference pricing exists, a natural extrapolation of changed medicine use (to the cheaper alternative) to reduced expenditure may not be evidenced. For example, reference pricing of histamine 2 receptor antagonists in British Columbia, Canada, initially achieved the goal of reduced expenditure on that class of medicines. However, reallocation of demand to proton-pump inhibitors was later observed, and an increase in co-payment by senior beneficiaries was also evident.\textsuperscript{20}

In Hungary where the statins were reference priced, an increased consumption (DDD from 1.14 to 1.64) occurred, with the consequence that the anticipated net savings were not achieved.\textsuperscript{118} The practice of using increased dosages of the new reference product, resulting in increased consumption, has been used as an argument against reference pricing in New Zealand,\textsuperscript{137} but without substantial evidence. Indeed, PHARMAC reports considerable savings through the use of reference pricing, although, due to the application of a mix of purchasing strategies it is difficult to distinguish the effect on expenditure that can be solely attributed to reference pricing.\textsuperscript{138}

Effect on Health and Health services Use

Evaluations of the impact of generic reference pricing in the available literature are largely limited to effects on cost and utilisation, and not health outcomes. Effects of switching between generic and brand versions of the same medicine are assumed to be largely unproblematic for the majority of the population as bioequivalence has already been established when the generic product is licensed or registered for use.\textsuperscript{139} Clinical trials are thus unlikely to be conducted for generics unless the preparation is one which has traditionally been considered non-bioequivalent; classically those medicines which have a low therapeutic index wherein the margin between efficacy and toxicity is small. Such medicines include for example anticonvulsants, antiarrhythmics, cyclosporine and warfarin; however some clinical studies have challenged the non-interchangeability of these medicines.\textsuperscript{24,140-142}

Comparisons between members of a therapeutic class to establish equivalence or superiority are ideally evaluated within randomised, double-blind, controlled clinical trials, and
may be conducted by pharmaceutical companies wishing to provide evidence of superiority of their preparation over another. Generally when a variant of an established therapeutic agent comes to market (also referred to as a “me-too” drug), it has some feature which possibly gives it an advantage over existing class members.

Evaluations of the effect on health outcomes of therapeutic referencing pricing are limited. Studies have been conducted in Canada, Germany, New Zealand and the United States of America, with the majority of examples being drawn from older (>65 years) British Columbia residents (see table 2.1 below).

The majority of participants have been drawn from over 65 year old Canadians living in British Columbia; one of the Canadian studies randomly selected participants to be included in the cohorts.143 Except for the New Zealand studies, pharmacy databases of insurers were used to select study participants and, where needed, were linked to other datasets to evaluate use of health services. The studies based in New Zealand selected individual patients and measured changes in blood pressure and hypercholesterolemia; however, these studies have methodological limitations primarily related to a lack of comparator groups and the number of measurements post-intervention.90

No evidence of increased mortality associated with reference pricing of nitrates, ACE inhibitors or calcium channel blockers was reported in the Canadian studies.144 Three of eight studies noted transient increases in the use of outpatient services (GP visits) but no difference in use of inpatient services.136,145,146 One study identified more overall hospitalisations (all-cause) but no significant difference in hospitalisation specifically due to the relevant coronary artery disease, or emergency or outpatient care for switchers.131

2.4. A summary of the evidence on reference pricing

Major price differentials (up to 80%) exist in the marketplace between an innovator brand and its generics. Generic reference pricing takes advantage of this and is generally successful in reducing prices in the short term, but may need additional policies or regulation to sustain it. A general trend of decreased consumption of the non-referenced product has been found. However, there is evidence of re-allocation of demand to alternative medicines outside of the cluster, as well as patients stopping therapy altogether or splitting tablets to avoid co-payment disincentives.
Table 2.1 Health outcomes of therapeutic reference pricing: published findings

<table>
<thead>
<tr>
<th>Country</th>
<th>Class affected</th>
<th>Health Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada 147</td>
<td>Nitrates</td>
<td>No increase in short-term use of rescue medicine (sublingual nitrate)</td>
</tr>
<tr>
<td>Canada 20,143</td>
<td>Histamine 2 receptor antagonists</td>
<td>No impact on health service use Increased cost-burden in elderly</td>
</tr>
<tr>
<td>Canada 130,148</td>
<td>ACE inhibitors</td>
<td>Transient increase in hospitalisations and GP visits Decreased admission to long-term care N/sig diff in mortality</td>
</tr>
<tr>
<td>Canada 133,148</td>
<td>Dihydropyridine calcium channel blockers</td>
<td>No impact on health service use</td>
</tr>
<tr>
<td>Canada 149</td>
<td>Nebulised bronchodilators</td>
<td>No impact on health service use</td>
</tr>
<tr>
<td>Canada 145</td>
<td>Proton pump inhibitors</td>
<td>No increase in hospitalisations, temporary increase in GP visits</td>
</tr>
<tr>
<td>Germany 149</td>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>Switchers hospitalised more often, but non/sig diff in hospitalisation due specifically to coronary artery disease, or ED visits, or outpatient care.</td>
</tr>
<tr>
<td>New Zealand 137</td>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>Decrease in lipid control</td>
</tr>
<tr>
<td>New Zealand 138</td>
<td>ACE inhibitors</td>
<td>11% of patients BP remained uncontrolled after 6 months</td>
</tr>
<tr>
<td>New Zealand 135</td>
<td>Dihydropyridine calcium channel blockers</td>
<td>No effect on blood pressure</td>
</tr>
<tr>
<td>USA 140</td>
<td>Anti-inflammatory agents</td>
<td>No increase in GI bleeds/inpatient endoscopies Increased rates of outpatient peptic ulcer disease</td>
</tr>
</tbody>
</table>

Evaluations of the effect on health of therapeutic referencing pricing are largely limited to the Canadian elderly living in British Columbia, with a few methodologically-limited studies based in New Zealand. Few studies have measured health outcomes for generic reference pricing. Very few studies examine direct health outcomes, with most examining health services use. Measurement of overall expenditure including cost of changes in health services use has largely been neglected.

2.5. Chapter conclusion

This chapter reviewed managerial strategies used to contain pharmaceutical expenditure. Targets and feedback mechanisms, formularies, capped budgets and co-payments all work towards influencing demand by prescriber and patient in this regard. Reference pricing is core to supply-side management strategies and has been used extensively, yet as a reimbursement policy also influences demand. The effect of reference pricing on market share and prices has been examined, suggesting that economic gains are short-lived unless accompanied by other strategies.
Effects of reference pricing on the patient however, have largely been neglected, leaving suspicion of non-equivalence and non-interchangeability, especially in key therapeutic areas, unchallenged.

New Zealand has a long history of reference pricing and is well-placed to examine the economic impact as well as clinical effects of generic reference pricing. The next chapter in this thesis describes in more detail the context of the New Zealand health sector and the management of medicines and strategies used to control expenditure.
Chapter 3. The setting – the New Zealand health sector

This chapter presents the current New Zealand health sector with particular emphasis on the access to medicines, and identifies features of the pharmaceutical sector which either directly influence, or have the potential to influence the choice of medicines.

3.1. The New Zealand population

Situated in the south-western Pacific ocean, New Zealand had a per capita GDP of US$29,334 in 2013, making it one of the World Bank-ranked high income countries. At the last census in 2013, the total population of New Zealand was estimated to be 4.24 million and this is expected to rise to 4.8 million in 2021, whilst also becoming more ethnically diverse and aged. One in 7 New Zealanders identify as Māori, one-third of whom are under the age of 15 years, whilst 1 in 8 people living in NZ are Asian (doubling since 2001), with almost two-thirds of the Auckland region being of Asian ethnicity. Hindi as a language is now the 4th most commonly spoken language, after English, Māori, and Samoan.

Like many other moderate to high income countries, the proportion of the New Zealand population aged 65 years and over is steadily increasing: in 1991 it was 11%, in 2009 the older generation accounted for 13% of the population and estimates suggest that by 2026 this will be higher still at around 19%.

The relevance of diversity of ethnicity and an aged population become apparent in examining the consumption of healthcare resources and economic and welfare resources of these sub-populations.

3.2. The Health of New Zealanders

Life expectancy in New Zealand, at around 81 years, is comparable to that of other OECD countries, whose average is 79.8 years. A slow trend of increasing life expectancy for both women and men is evident. In the 80’s, life expectancy was 76 years for women and 71 for men; by 2012 this has increased to 83 and 79 years respectively. There is, however, an ethnic disparity between Māori people and non-Māori. Data from the 2005-2007 period place life expectancy for Māori people 8 years lower than that of non-Māori people, and 7.3 years in 2012.

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1 In comparison, Australia had a per capita GDP of US$37,491 and Canada US$37,528 for the same year.150
This skewed pattern is seen in other key health statistics, with Māori people consistently having a lower health status than non-Māori.\textsuperscript{154}

The 2011/12 New Zealand Health Survey describes an upward trend for the adult New Zealand population with respect to obesity, hypertension, hyperlipidaemia, diabetes and mental health-related disorders, (see table 31 below);\textsuperscript{155} such conditions either directly or indirectly require pharmaceutical intervention in addition to other medical and lifestyle management.

Table 3.1: Key health indicators (% of population by year)

<table>
<thead>
<tr>
<th>Condition</th>
<th>2008</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Doctor diagnosed diabetes</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Obesity</td>
<td>26%</td>
<td>28%</td>
</tr>
<tr>
<td>Asthma (children)</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Asthma (adults)</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Mood disorder (mostly depression)</td>
<td>10%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Source: Ministry of Health, NZ.\textsuperscript{155,156}

\section*{3.3. An overview of the New Zealand health system}

New Zealand operates a publicly funded health system, with about 80% of all healthcare needs funded by the state, a smaller portion (16.8% in 2010) met by out-of-pocket payments and private health insurance, and a minor amount met by not-for-profit organisations.\textsuperscript{157} As a portion of gross domestic product, expenditure on health has been around 10% in 2010, 2011 and 2012.\textsuperscript{71} In 2014, the annual government expenditure on health was nearly NZ$15 billion out of a total government expenditure of NZ$92 billion, the second highest budgetary item.\textsuperscript{158} For the same period, expenditure on social security and welfare was the highest (NZ$23 billion), with expenditure on education (NZ$12 billion) just less than health.\textsuperscript{158}

New Zealand’s public health and disability sector is primarily driven by central government expectations of the 20 District Health Boards (DHB) who are the planning and purchasing units in each geographically defined district. These boards are responsible for the provision and/or purchase of healthcare services through service agreements with a range of providers including doctors at primary care level through Primary Health Organisations, and private pharmacy, laboratory and other services, as well as public hospitals and tertiary hospital care. In addition, some community and homes-based services are also provided by the DHBs.\textsuperscript{157}

As successive governments have imprinted their own fundamental policy beliefs on health service delivery, there have been variations in the system with regard to the number of administrative boards (now the DHBs), lines of reporting and funding and the extent of service
agreements and private sector involvement.\textsuperscript{159,160} Philosophies underlying each successive change have varied around the extent of centralisation of funding and decision-making, how market- and efficiency-based and target-driven service provision should be, and the relative priority given to preventive and curative services. The post-2008 health system has focused on performance, reduced inefficiencies and bureaucracy, improved regional and national co-ordination, and reduced waste.\textsuperscript{159}

However, the primary healthcare service provided by the doctor, nurse and pharmacist with whom the majority of patients interact, remains largely unchanged. A patient still makes an appointment with a doctor for non-life threatening health needs; they are referred to other services such as radiography as needed, or to a hospital for more specialized care; and they still collect their prescriptions from the pharmacy. It is within the chain of service delivery from the issue of a prescription to the collection of the medicines – the NZ medicines system – in which the focus of this thesis lies.

3.4. The New Zealand Medicines System

Prior to 2007, no overarching medicines policy was well formulated or documented,\textsuperscript{161} however, in 2005 New Zealand commenced establishing a policy and consequently published the ‘Medicines New Zealand’ document. This strategy document is accompanied by ‘Actioning Medicines New Zealand’ and details the implementation of the policy and describes achievements toward the policy goals to date.\textsuperscript{162}

Three broad areas are described in the policy to achieve the delivery of:

1. quality, safe and effective medicines
2. equitable and affordable access
3. optimal use of medicines resulting in optimal health outcomes.\textsuperscript{161}

The demarcation of these policy objectives is used in the following sections to describe the landscape of the medicines systems in NZ.

3.4.1. Policy objective 1: Quality, safety and efficacy

\textit{Registration of medicines and Pharmacovigilance}

Ensuring that medicines reaching the New Zealand market are of good quality and are both safe and efficacious is achieved via rigorous regulation of the product before allowing it to enter the market and via continual post-market surveillance or ‘pharmacovigilance’. These roles
are filled in New Zealand by the Medicines and Medical Devices Safety Authority (Medsafe) and the Pharmacovigilance Centre for Adverse Reactions Monitoring (CARM).

Medsafe is the business unit within the Ministry of Health responsible for administering the Medicines Act 1981 and Regulations 1984 and thereby the regulation of medicines and medical devices in the country. More broadly, Medsafe is responsible for determining which medicines will be available for sale in New Zealand and under what conditions, and is also able to deny registration. It ensures that information data sheets for every prescription medicine and pharmacist-only medicine are prepared in accordance with regulations. Medsafe also monitors adverse reactions to medicines used in New Zealand whilst at the same time scrutinising international safety information.

The New Zealand Pharmacovigilance Centre for Adverse Reactions Monitoring (CARM) actively monitors selected new medicines. CARM also receives and analyses spontaneous reports of adverse events from the public and medical practitioners.

Classification of medicines

The availability of medicines in New Zealand depends on its classification by Medsafe in accordance with the Medicines Act. If a preparation makes a therapeutic claim or contains an ingredient listed in any of the First Schedule of the Medicines Regulations 1984, the Schedules in the Misuse of Drugs Act 197, or the Medsafe list of general sale medicines, it is classified as a medicine and will have certain regulations attached to it.

Some medicines are available in a supermarket, based on considerations of the active ingredient, strength and package size. For example ibuprofen is available in a supermarket at 200mg strength in a pack containing not more than 25 doses. Larger pack sizes of the 200mg strength are available from pharmacies only, and ibuprofen 800mg/dose is prescription-only medicine available only in a pharmacy and dispensed only with a doctor’s prescription. Natural products such as St John’s wort, are not considered medicines so long as they do not make a therapeutic claim, and are not governed by Medsafe’s regulatory process.

Professional competence

Quality assurance with respect to the pharmaceutical professional is provided by the professional organisations and standards of practice required by them. Primarily these are the Pharmacy Council, the Pharmaceutical Society and the Pharmacy Guild; however, there are other organisations which serve sub-sections of the profession such as the Hospital Pharmacists Association and the Clinical Advisory Pharmacists Association.
The Pharmacy Council oversees the registration of pharmacists under the Health Practitioners Competence Assurance Act 2003, and any disciplinary action thereto. Membership of the collegial Pharmaceutical Society of New Zealand is voluntary; however the Society is contracted by the Pharmacy Council to provide and monitor mandatory continuing professional development of all practising pharmacists. The Pharmacy Guild is a membership organisation which provides support and services to community pharmacy proprietors. A major activity of the Guild relates to acting as an agent for its members in matters relating to contractual agreements with DHBs.

3.4.2. Policy objective 2: Equitable and Affordable Access

The ‘Medicines New Zealand’ policy aims for New Zealanders to have universal access to healthcare including “access to medicines they need, regardless of their individual ability to pay.” Yet notes that this access must lie within the limits of a capped medicines budget.

This policy objective is important in the context of this thesis and is expanded on further in the following sections.

The Pharmaceutical Management Agency (PHARMAC)

PHARMAC was established in 1993 by the four Regional Health Authorities (which were responsible for purchasing health services for their populations) to contain the ever-increasing costs of medicines by utilising bulk purchasing power and other bargaining strategies. In 2000 PHARMAC was established as an independent Crown Agent under the New Zealand Public Health and Disability Act, 2000 and in its current form, responsibility for PHARMAC falls directly under the jurisdiction of the Minister of Health. The Chief Executive Officer of PHARMAC as well as the Medical Director and members of the Board are all appointed by the Minister of Health.

Although some organisations and agencies within the health system have disappeared or significantly changed, PHARMAC has stood the test of time and has seen its responsibilities increase over the years. Initially, PHARMAC was a unit which negotiated procurement of medicines on behalf of the Regional Health Boards, whereas it now has a mandate to manage the community pharmaceuticals budget and vaccines, and hospital pharmaceutical and medical device procurement.

PHARMAC’s mandate as defined in the NZPHD Act, 2000 is:

..To secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the funding provided.
[And] to maintain and manage a pharmaceutical schedule that applies consistently throughout New Zealand, including determining eligibility and criteria for the provision of subsidies.\textsuperscript{164}

Acting on behalf of the DHBs, PHARMAC is responsible for defining the annual Community Pharmaceutical Budget and expenditure against this capped budget; one of the major achievements attributed to PHARMAC is its ability to contain expenditure in an increasingly expensive and complex pharmaceutical market and an upward trend of demand. In 2013/14 expenditure on community pharmaceuticals was NZ$795 million, paying for 42 million prescription items to 3.4 million NZ patients.\textsuperscript{165}

The Pharmaceutical Schedule

A key tool used by PHARMAC is the formulation of a limited list of pharmaceutical preparations which are subsidised by the government and included in the Community Pharmaceutical Schedule (“Schedule”). The Schedule is a positive list of subsidised medicines listed by therapeutic category, together with any special eligibility or prescribing conditions. In compiling this list, PHARMAC is supported by a committee of senior health professions drawn from wide ranging specialities, whose primary function is to advise on applications for inclusion of new preparations to the Schedule. This Pharmacology & Therapeutics Advisory Committee (PTAC) formally considers the evidence for a new entity and applies nine established criteria before making a recommendation to the PHARMAC board.\textsuperscript{163} Aside from clinical efficacy, these criteria include considering the impact on the annual pharmaceutical budget, any potential cost to the patient and specifically, the needs of Māori and Pacific peoples.

Preliminary recommendations from the advisory committee are then further considered by the PHARMAC Board who makes opportunity-cost and budgetary decisions following consultations with the relevant pharmaceutical companies before listing a medicine in the Schedule.

PHARMAC Pricing policies

To achieve the balance between meeting the recommendations of the PTAC and the wider medical profession and patient demand, PHARMAC employs a number of negotiating and contracting strategies with pharmaceutical suppliers.

For preparations where the patent for the originator brand has expired and multiple generic equivalents exist, PHARMAC uses a mix of generic reference pricing, tendering and direct negotiation for the award of contracts to procure medicines efficiently. PHARMAC invites manufacturers to bid against each other with the promise of winning a contract to supply the NZ market for a fixed period of time. This “auctioning” (Morgan, 2007) style of price negotiation is
made possible by PHARMAC holding a monopsony over the entire funded pharmaceutical market and achieves considerable price reductions.40

For newer preparations PHARMAC uses other strategies with pharmaceutical suppliers to achieve mutually accepted prices. If the supplier has other preparations already listed in the Schedule, PHARMAC will agree to list a new product if the supplier reduces the price of its other product(s) in a ‘bundling’ or ‘cross-product’ arrangement.138 This leaves the listed price of the new preparation at the manufacturer’s international price, indirectly subsidised by a second product. Similarly, a risk sharing agreement can be used to introduce a new preparation in the Schedule whereby PHARMAC protects the budget against unexpected high consumption and expenditure. A limited sale level is agreed with the supplier and if sales exceed this level, the supplier agrees to cover the costs through a rebate to the DHBs. This again leaves the manufacturer’s international price intact, which is important to the manufacturer as other countries use NZ prices as a benchmark against which to set their own prices.91 In addition, PHARMAC sometimes awards contracts at prices lower than a product’s international price in exchange for future price-protection.

PHARMAC has a ‘Special Authority’ system (SA) in place whereby access to a certain preparation must be requested before supply to a patient will be funded.166 A preparation list in the Schedule may have certain prescribing restrictions attached to it limiting the conditions for supply and the level of specialisation required of the prescriber. Such a mechanism limits the use of the pharmaceutical for both budgetary and safety reasons whilst at the same time providing a safety net offering patients access to the product, and diminishing the risk of controversy and public lobbying that denied access might otherwise create.

The SA restriction is commonly applied to new listings in the Schedule; however at times the restriction remains in place for a particular brand of medicine, even once generic equivalents have been approved for subsidy. This continued subsidy of a particular brand under SA rules has the effect of diminishing the incentive to switch to using a generic brand.

**Negative list, Exceptional Circumstances and Section 29**

There is no ‘negative’ list in New Zealand, i.e. a list of those pharmaceuticals which are not funded, generally because of proven inefficacy. By default if a preparation is not in the Schedule it is not funded, unless exceptional circumstances exist in which case there are separate funds and processes to secure funding.167

There are certain medicines which under the Medicines Act require a prescription for their use, but which are not listed in the Schedule. Such medicines may be registered by Medsafe for use in NZ, or might be imported and dispensed on a ‘named-patient’ basis under Section 29 of
the Act. These items are generally not subsidised and dispensed at a total cost to the patient. Section 29 items have included for example, amiloride and melatonin, but might also include ‘orphan’ medicines used in rare conditions.

Dispensing of prescription medicines

There are some 1000 pharmacies in New Zealand and about 3000 registered pharmacists, 75% of whom work in the community setting, and 12% in the hospital pharmacy sector. Ownership has changed considerably from the 1990s. Previously, 75% of the share capital of a pharmacy had to be held by a pharmacist and each pharmacist could only hold shares in one pharmacy. Changes to the Medicines Act now allows the construction of pharmacy chains and corporate pharmacies, the share ownership of which is more complex and requires 51% of the shares to be held by a pharmacist who can however hold shares in up to 5 pharmacies. Several pharmacies are also owned in which the majority of the remaining 49% of shares is held by a pharmaceutical wholesaler.

Accessing prescription medicines first requires a prescription from a registered doctor or other authorised prescriber (for example a dentist, midwife or prescribing nurse) before dispensing at a community pharmacy. New Zealand does not permit doctors to routinely dispense medicines as is the practice in some other countries, although doctors serving more remote areas can issue medicines under a Practitioner’s Supply Order.

Community pharmacies in New Zealand are privately owned, holding a contract with one of the District Health Boards to provide defined services. The contracts detail services which will be reimbursed and primarily includes the dispensing of medicines, but also includes the provision of services to Community and Alcohol Drug clients, and the preparation of infusion pumps, for example. Pharmacies are reimbursed by the DHB for prescriptions dispensed in the previous two weeks, and payment includes the scheduled cost of the medicines, a small mark-up (to cover the costs of storage and wastage) and a fee for dispensing (which includes the degree of difficulty of preparation and use of containers). The patient contribution (co-payment) is subtracted from the reimbursed amount, as this is collected by the pharmacy at the time of sale.

In late 2012 DHBs started contracting pharmacies to provide services to patients with significant chronic illnesses who need more intensive monitoring and intervention. Under the contract, services including single-dose packaging of medicines and monitoring and medicines reviews are provided for a single annual capitation fee paid to a single pharmacy for that patient.
Cost of medicines to patients

Patients make a co-payment per prescription item, whilst the government bears the cost of the medicine from the manufacturer for those items listed in the Schedule. Patient contributions have changed from an initial maximum of $1 per prescription item to $5 in 1988, $15 per item in 1991 (with concessions to minimise the burden of co-payments to low-income families and people with multiple co-morbidities), $3 per item in the mid-2000s and $5 per item again in 2013, with no concession for low-income families.\textsuperscript{169} Prescriptions for children under 6 require no co-payment.

The maximum amount any adult or family should currently have to contribute is $100 per year, as there is a maximum number of 20 prescription items per year per family for co-payment, after which no co-payment is required for the remained of the calendar year.\textsuperscript{39} However, despite the availability of certain safety nets, the Ministry of Health found in 2011/12 that around 8% of prescriptions were not filled due to cost.\textsuperscript{155} Similarly, a higher burden amongst Māori and Pacific people has been reported, with 14% and 15% respectively of whom deferred collecting a prescription (at $3 co-payment per item) in 2004.\textsuperscript{80}

For a minority of items in the Schedule listed as not fully subsidised a part-charge will be payable by the patient (for example brand specific preparations, where a generic brand is fully subsidised, such as salbutamol inhalers). Prescription items not listed in the Schedule must be paid for in full by the patient.

Data reported by the Ministry of Health using the system of health accounts developed by the Organisation for Economic Co-operation and Development (OECD), indicates out-of-pocket expenses in 2010 accounted for around 30% of total expenditure on pharmaceuticals and other medical non-durables, and was higher than France, Canada and the USA for that time period.\textsuperscript{157,170} This category of expenditure incorporates prescribed and over-the-counter medicines and “other medical non-durables”; however, a breakdown by each of these is not given and an interpretation of the figure is difficult as it is unclear what proportion of the amount is accounted for by over-the-counter medicines and whether these purchases have been recommended by a doctor as necessary. In addition, what constitutes the ‘other non-durable’ category is not defined.

Generic Substitution

NZ does not have an explicit generic policy; no regulations exist for example on the labelling of medicines with their generic name, or on the name used in a prescription or within healthcare data systems. In 1988 a change in the Medicines Regulations was signalled by the Minister of Health, David Caygill, to allow the practice of generic substitution.\textsuperscript{106} In July 2011,
regulatory changes were finally made to permit substitution of a prescribed brand product with a generic equivalent, unless the prescriber has specifically instructed a substitution not to be made. In practice, pharmacists have been substituting the brand as prescribed for the available fully-subsidised brand, mostly a generic, for many years. Regulations prior to 2011 required that such substitutions were either endorsed per prescription by the prescriber, or that the pharmacist had been given written permission to make substitutions by each prescriber.

There has been considerable resistance to the regulation and to generic substitution in general. The pharmaceutical industry is active in resisting the introduction of generics onto the market for obvious reason,\textsuperscript{106} and as companies in New Zealand are able to market their products and opinions directly to consumers (similar only to the US) it is not surprising that consumers in New Zealand have little understanding of generic medicines.\textsuperscript{51} Misinformation and suspicion is commonplace amongst pharmacists and doctors on the bioequivalence and hence on the substitutability of generic products.\textsuperscript{52,171}

Aside from misconceptions about generic bioavailability, NZ pharmacists have little incentive to make substitutions to a less expensive product. Payment for the products they dispense incorporates a percentage mark-up on the base cost, and hence the more a product costs, the higher the actual return. In the past this mark-up was significant (50\% in the 1940\textsuperscript{s}\textsuperscript{169}), whereas it is now around 3-5\%. The incentive remains today, albeit on a diminished scale and only where there are multiple brands listed in the Schedule at different manufacturer’s base cost (for example there are multiple brands of lamotrigine).

As successive innovator brands come off patent, and PHARMAC lists the significantly cheaper generic alternative, income for prescriptions diminishes for the retail pharmacy. For example atorvastatin was available only as the innovator Lipitor brand at NZ$18 for thirty 10mg tablets in 2008,\textsuperscript{172} the generic form in 2012 was less than NZ$1 for the same thirty tablets, and hence the returns have decreased 18-fold.\textsuperscript{173}

Other issues influencing a pharmacist’s decision on substitution include the increased investment and management in stocking multiple brands and the subsequent potential for waste due to expiry, and by discounts and rebates awarded by wholesalers, who themselves might be a share-holder in that pharmacy and which are generally not passed on to either the consumer or the government insurer.\textsuperscript{169}

If a patient does not want the generic or Schedule-listed brand, they are required to pay (either in full or the difference in cost) for another brand. This raises an oft-used argument against substitution policies: that of consumer and prescriber freedom of choice\textsuperscript{110} (and hence also of equity, since only those who can afford to pay the difference will have the choice).
PHARMAC has responded to the uncertainty around brand substitution and has undertaken several activities to increase awareness of brand changes. A leaflet explaining brand switches (“My medicine looks different”) is distributed to patients through NZ pharmacies and medical practices. Patient-specific literature is available on the PHARMAC website, and educational meetings have been held to assist pharmacists in explaining changes of medicines for mental health conditions. In addition, pharmacists are reimbursed per patient for the additional time they need to counsel patients on product-specific changes (called a ‘brand switch fee’).

A series of problematic product changes occurred in 2007-2009, with pharmacists complaining about the burden of explaining changes to patients.54 The formulation of the Eltroxin brand of levothyroxine changed in mid-2007 in New Zealand, as it did in Germany, the Netherlands and Singapore also; yet only in NZ did patients report adverse events.48 A change in the funded brand of omeprazole from originator Losec to a generic brand174 also created dissent amongst patients.54

On the 1st December 2010, PHARMAC implemented payment of a ‘Brand Switch Fee’ in recognition of “the additional counselling required for switching patients between brands of certain medicines...”175 The fee (as an additional dispensing fee) is payable once per patient only, to the pharmacy when a patient switches brands,175 and amounts to approximately NZ$5 per patient (NZ$4.76 for erythropoietin, NZ$4.33 for risperidone, for example).63 This brand switch fee payment continues to date and, as an incentive, may have now become an almost de facto payment. Between December 2014 and February 2015 brand switch fees could be claimed for olanzapine, quetiapine, capecitabine and citalopram, and for erythropoietin and risperidone in February and May 2015 respectively.63 Prior brand switch fees have been applied to enalapril, captopril, tacrolimus, lamivudine, zidovudine with lamivudine, entacapone, losartan, terazosin, ipratropium bromide, azathioprine, and blood glucose meters amongst others.

3.4.3. Policy objective 3: Optimal use for optimal outcomes

A considerable amount of money is spent on powerful, but potentially harmful medicines and it is important that they are used optimally. ‘Optimal use’ thus includes appropriate prescribing, use as intended, and minimisation of misuse and waste.

Appropriate prescribing

Monitoring the patterns of prescribing at the level of individual medical practice is undertaken by the DHBs with information being published annually, as a form of self-audit. Data
from PHARMAC indicate the number of prescriptions written annually continues to rise, with nearly 40 million community funded prescriptions dispensed in 2010/11, representing a 7% increase over the previous period. More than half a million adults were taking medication for high blood pressure in 2011/12 (one in six adults) and some 300,000 adults (one in 10) took medicines for cholesterol management.

**Appropriate use**

Appropriate use of medicines by patients (historically called “patient compliance”), is reliant on an understanding of the disease process and of the place in therapy of their medicines; such information can be gained from multiple sources ranging from the medical fraternity to the internet, radio and other media, and friends and family. The role of the pharmaceutical industry in information provision in NZ cannot be ignored. Direct-to-consumer advertising is not permitted in any EU country other than NZ and the USA in recognition of the potential bias such information contains.

Factors identified in studies as influencing adherence to therapy include patient characteristics, the condition being managed, medication costs, health beliefs and provider communication.

A Cochrane review of studies on improving patient adherence to therapy suggests that, for whatever reason, a large proportion of patients do not take their medicine as prescribed. Studies included in the review report adherence ranging from 0% to 100%, with an average of 50% of patients being adherent. The review also found that interventions to improve adherence were complex and might be difficult to replicate in the non-experimental setting, and the benefits reported were small.

**Wastage**

DUMP campaigns have been conducted in several DHBs in New Zealand. These are campaigns designed to encourage patients not to dispose of unused medicines in the usual waste disposal system, but to return them to a pharmacy for environmentally secure disposal. The campaigns take the opportunity to collect information about the reasons for the returns, and, aside from death, were due in part to medication changes, the medicine no longer being required or having expired. In the majority of instances, more than 75% of the original amount dispensed was returned for disposal, an amount which can be considerable since New Zealand has a ‘stat’ dispensing policy which sees a 3-month supply period being dispensed at one time.
The pharmaceutical industry

In terms of trade exports, the pharmaceutical industry in NZ is small and is not a major contributor to the national GDP of $229.7 billion (2013). A small number of New Zealand pharmaceutical manufacturing companies exist (approximately 12), with two companies accounting for the majority of the revenue generated (of the order of NZ$50 million/year). The larger companies are concerned with the manufacture of existing medicines (primarily generic medicines) and of intermediate compounds and ingredients; whilst the bulk of the small companies are involved in drug development of new entities. In 2008 twelve such NZ-discovered compounds were in the stages of clinical development.

The role of the pharmaceutical industry lies primarily in bringing pharmaceuticals to the New Zealand market. Medicines New Zealand™ (MNZ) is the transformed organisation of its predecessor, Research Medicines Industry (RMI), and represents eighteen international pharmaceutical companies engaged primarily in the prescription medicines’ market. None of the indigenous NZ companies are listed as members of MNZ.

The Trans Pacific Partnership Agreement (TPPA) under consideration by NZ is a trade agreement which involves 12 countries including the USA. Under this agreement, the details of which remain confidential from public scrutiny, proposals exist which seek to establish policies related to trade with pharmaceutical companies. From leaked discussion documents, there appears to be a focus on pharmaceutical intellectual property rights, extensions of these rights and dispute mechanisms which have potential implications for the mechanisms which PHARMAC uses in negotiating prices of preparations. The final text of the TPPA and any potential impact remains unknown, with the negotiations still ongoing in 2015.

Medicines availability, timeliness of new entity entry into the market

The appearance of new pharmaceutical preparations in the market is dependent on a number of factors. In the first instance, the manufacturing company will initiate a launch based on expected uptake and profit, and thus must take into consideration any costs and likely benefits associated with the introduction of the product such as the size of market and, in the case of New Zealand, the likelihood of that preparation being included in the Schedule and hence funded by the government, or any restrictions that might be placed on its sale. The cost of registering a medicine in New Zealand can be considerable: the application fee for a

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* The organization should be distinguished from the overarching government policy for medicines in New Zealand also called ‘Medicines New Zealand’.
prescription medicine to be considered for registration by Medsafe is between NZ$ 40 and NZ$80 thousand.\textsuperscript{185}

Delays in launch are not unique to New Zealand or indeed, to many other countries, with some notable exceptions. Of 24 OECD countries, Japan stands out as a country in which there is almost simultaneous launch of a new molecule following its world launch and in Denmark, Switzerland, Sweden and the UK, the majority of new preparations are launched in less than 18 months from the date of the first global launch.\textsuperscript{69} New Zealand has been compared with Australia, Canada and Finland with regard to launch lag times and medicines availability.\textsuperscript{17,19,40} Overall, New Zealand funds fewer members of a single therapeutic class (‘me-too’ products)\textsuperscript{40},\textsuperscript{186} with longer lag times to launch.\textsuperscript{17-19,69} Between 1986 and 1992 a total of 122 new molecules were launched internationally, and of these 36 were available in New Zealand by 2002.\textsuperscript{69}

The health effects of delayed launches and fewer medicines within a therapeutic class have been debated but remain unmeasured.\textsuperscript{186,187} One aspect included in the negotiations for the TPPA is the issue of compensation for delays in launch, with the pharmaceutical industry seeking to extend the patent period for any launch delays.\textsuperscript{188}

\textbf{3.5. Chapter Summary}

Like many other OECD countries, New Zealand’s pharmaceutical sector has its own nuances, but is focused on delivering safe and affordable pharmaceuticals to meet the needs of the New Zealand population. Although criticisms of the health system and particularly the medicines supply system exist, New Zealand does not fare worse to any great degree than its OECD counterparts in terms of life expectancy, availability of medicines or pharmaceutical expenditure.

Key features of New Zealand’s medicines sector are the place of the privately-owned community pharmacy in the government funded delivery of medicines, the use of cost effectiveness technology assessments, capped annual budgets and the extensive use of referencing pricing to achieve policy objectives.
Chapter 4. Study Method Part 1

4.1. Introduction

The previous chapters reflect on the practice of generic reference pricing, on the available evidence base for its effectiveness in reducing pharmaceutical expenditure, and on concerns of bioequivalence of generic medicines. The question “Do NZ patients who switch brands because of generic reference pricing, fare worse than non-switchers?” was posed, and the suitability of the New Zealand setting to research this question was described.

This chapter now describes the approach taken to investigate the specific objectives of the study, particularly Part 1 objectives which relate to evaluating the effect of reference pricing of certain exemplary medicines on:

- patients’ patterns of medicine usage
- health outcomes of switching from one brand of medicine to another
- associated health services utilisation and costs.

The rationale for choosing the particular retrospective observational methodology is described, before elaborating on the study design, data sources, and data collection and analysis.

The survey methodology which was employed to gain insight into the patients’ perspective on switching between medicines, including understanding their reasoning for switching or not, describing additional or hidden costs borne by the patients, and evaluating their willingness to pay for an alternative choice, is described in Chapter 6.

4.2. Rationale for study methods employed

In the evaluation of one medicine against another, prospective randomised controlled trials (RCT) are regarded as the ‘gold standard’. The strength of RCTs lies in the randomisation of participants to experimental groups and blinding of both participants and evaluators to this process, which serves to reduce selection bias and confounding. However, head-to-head RCTs are rarely conducted to evaluate a generic version of a medicine against its innovator analogue, especially considering that they must already have demonstrated bioequivalence to be eligible for registration. Similarly, RCTs are rare in the evaluation of policy interventions such as reference pricing. Uniquely, Schneeweiss and colleagues (2014) were able to persuade British Columbia’s provincial medicine benefits agency to delay the implementation of a change in policy on nebulised medicines for randomly selected clusters of doctors and
patients for 6 months, allowing them to conduct a randomised trial on the clinical and economic effects of the policy.\textsuperscript{149}

Although theoretically possible in the NZ setting, conducting a randomised trial to evaluate the clinical effects of reference-pricing policies and brand substitution would have posed significant practical and ethical problems potentially beyond the scope of a doctoral study, requiring the co-operation of multiple levels of governance. Prescribers and pharmacists would have had to be persuaded that such a study would not create unnecessary administrative burden or financial disadvantage, whilst consent from patients and patient advocacy groups would have been required. In addition, the possibility of affecting the monopsonistic power PHARMAC holds as a single-purchaser and the implied costs would have had to be countered by the potential advantages offered by such a study’s outcomes. In the BC study, Schneeweiss et al (2014) were able to demonstrate that the cost of delaying the implementation of the new policy in 10\% of medical practices would equate to only an extra 18 days at the current policy expense (being 10\% of 6 months), and hence gained the funder’s consent.\textsuperscript{149} The use of an RCT to evaluate the impact of reference pricing at therapeutic class level in NZ might well be justified where clinical concerns of substituting one chemically distinct preparation for another exist, and could be considered for future NZ studies.

Observational studies and natural experiments within ‘real world’ populations, however, offer an opportunity to evaluate policy interventions as an alternative to prospective randomised trials.\textsuperscript{190-192}

4.3. Study design and data analysis

To evaluate the effect of brand switching on health service use, this study used an epidemiological approach. Methodological guidance for undertaking and reporting natural experiments and observational studies has been published, including the ‘Strengthening the Reporting of Observational Studies in Epidemiology’ (STROBE) statement,\textsuperscript{67,68,193} and was used in this thesis and in reporting the Part 1 findings.

Observational studies are, by definition, studies in which randomisation of participants to intervention and no-intervention group has not or cannot be done by the researcher.\textsuperscript{193,194} Primarily due to this lack of randomisation, selection bias and the potential for confounding are weaknesses of this type of study, which need to be countered within the study design and analytical methods employed. An observational study must overcome the possibility that the occurrence of some event other than the intervention is responsible for the observed outcomes, and ideally employs examination of the counterfactual in, for example, a time-series design, or difference-in-differences, matching or regression discontinuity analysis.\textsuperscript{195} In assigning causality
the design must counter the ‘fundamental problem of causal inference’ – that the same unit of study (the patient) cannot both be exposed and not exposed to the intervention - and make assumptions in estimating the designated counterfactual.\textsuperscript{196}

Time-series methodology has been used in a number of studies examining reference pricing, especially when considering changes in defined daily dose (DDD) as a measure of consumption, and was initially considered a viable approach to examining health outcomes for the studies in this thesis. However, a preliminary examination of the data suggested the low incidence of events for each individual patient (use of emergency services, hospitalisations and referrals to specialist services) would give wide variation in confidence limits and hence less precision for the outcome measures. Yet, in aggregating the data to overcome this issue, the opportunity to exploit advantages of having patient level paired data would have been missed. Hence a ‘difference-in-differences’ analysis was conducted in the case studies, using paired data to make comparisons for individual patients before and after the policy intervention, and to compare the differences for switcher patients with the non-switcher patients’ differences. The difference-in-differences design removes biases that could result from the two groups being fundamentally different as well as the intragroup influence of time and other coincident interventions (a parallel trend assumption), as these would be expected to occur equally in both groups. The design makes the assumption that the mean before-after variation for each group would have been the same had the intervention not taken place,\textsuperscript{67,195} and is marginally stronger than a ‘triangle design’ (post versus pre versus control) which does not account for temporal influences on the control arm.\textsuperscript{197}

In the difference-in-differences approach as used in this thesis, the counterfactual exists in patients who are policy non-compliers and do not switch to the fully funded medicine. A counterfactual of the effect of no reference pricing policy could have been constructed, for example including in the analysis a control group of patients taking a different antiepileptic or antipsychotic medicine; however, non-implementation of a policy is not the focus of the research question and such a design introduces other biases which would require statistical or other explanatory resolution.

The influence of measurable variables on selection (or assignment) to the switcher or non-switcher groups was visually explored using directed acyclic graphs,\textsuperscript{198} and then estimated using statistical regression of the available data against outcomes. Further analysis was undertaken to examine the combined effect of confounders, as well as potentially identifying patients who are likely to switch brands. Furthermore, propensity score matching was also used in the venlafaxine study; (see Findings: Venlafaxine, section 5.4).
4.3.1. Limitations of Observational Studies

Where a choice exists of using one medicine brand over another, selection bias must be expected as those making the choice – patients, prescribers or pharmacists - will naturally exert their preferences in the decision-making. Rubin (2008) underlines the need to understand the ‘assignment process’ and to accommodate this in the study design if selection is not to bias explanations of causality.\textsuperscript{30} The propensity or likelihood to switch has been explored in reference-pricing studies in BC, Canada, where attributes of age, gender, perceived severity of illness and cost of medicine and income were shown to influence switching behaviour amongst patients.\textsuperscript{135,199} This study searched for evidence of selection bias, examining as many between-group baseline attributes as possible within the available data, from patient attributes to, for example, prescriber and pharmacy loyalty.

Estimates of association between a factor (in this case changing between brands of medicine) and an observed outcome may be biased if confounding influences - such as patient attributes - are not accounted for.\textsuperscript{192} The presence of explicit, measurable confounders can be determined by examining known or suspected attributes of the cohorts included in a study; however, hidden or unknown confounders may persist and bias the strength of inferences drawn.\textsuperscript{200} This study used a self-controlled design, measuring outcomes in the same person during exposed and unexposed periods to minimise the influence of such confounders.\textsuperscript{192,193} The consequential risk, however, in using the same patient in a before/after type of design lies in survivorship bias. Such bias would exist if those patients who died before having the opportunity to switch brands would have systematically chosen one option (switching or not-switching).\textsuperscript{201} Survivorship bias within this study should be understood in terms of the inclusion criteria requiring patients to have been taking the study medicine for a one year period prior to the index date, and the measurement of ‘death up to one year after the intervention’, as an outcome.

4.3.2. Electronic healthcare databases

Acknowledging the potential weaknesses of observational studies, there are strengths which can be drawn on in using healthcare databases as the primary source of information for such studies. The recording of medical encounters and interventions in electronic form makes available large depositories of data for ‘epidemiological mining’, which, if attention is given to the limitations of the data, can provide a wealth of information.\textsuperscript{190}

Such databases are broadly of two kinds: those of an administrative nature used for reimbursement purposes and those primarily used to capture information at the point of care, recording health status, procedures conducted and diagnoses. One global issue related to
information within databases is the recognition that data will contain inaccuracies and omissions. Data entry that determines subsequent reimbursement may be more accurate than data which is based on patient recall; however, each type of database will have its own limitations, and the limitations of the specific NZ databases used in this study are considered in the sections below.

Neither a randomised controlled trial nor an observational study can, however, provide insight into a patient’s decision-making processes. One of the objectives of this study was to measure the receptivity of patients to alternative funding mechanisms, including paying for choice of brand and their understanding of brand-switching in general. For this reason, a cross-sectional survey was conducted in this study using a self-administered questionnaire. The study protocol and details of the survey is dealt with separately within this thesis, as submitted for consideration by the Australian Health Review journal, (see Chapter 6).

For the observational study, a process was developed for the identification of patients and extraction of health data which is hereinafter further described. The process initially involved meeting with the information analysts in the Ministry of Health’s Analytical Services unit to understand the breadth, depth and limits of the health data collections. An algorithm for data extraction was designed and tested, with modifications incorporated before the extraction was completed for the four selected study medicines.

4.4. Choosing the Study Medicines

Although medicines for acute and chronic clinical conditions have been subject to reference pricing in NZ, and could be considered to have equal clinical standing, this study focused on medicines for chronic conditions only. Evaluating the clinical outcomes consequent to medicines such as antibiotics, for example, used for short or intermittent periods of time, would likely involve quite a different study design and different outcome measures. Additionally, those medicines which consume a greater portion of the community pharmaceutical budget are those in which lies the potential for greatest savings, and hence this study’s focus.

4.4.1. Lamotrigine

Lamotrigine was initially selected for inclusion in this study as a ‘proof-of-concept’ to test the feasibility of the process. Generic reference pricing had been applied on 01 February 2007 by PHARMAC, with the introduction of two generic lamotrigine products into the Schedule which cost around half the price of the originator brand. Five months after the introduction of the generics, the agreed subsidy of the originator brand was reduced to almost the same as the generic equivalents and, in 2008, a third generic lamotrigine was introduced with a subsequent
decrease in price of the earlier two generics; the originator brand however remained at July 2007 prices. This situation meant that there would be patient level data available for at least two years after the 2007 index date, yet the referencing and any subsequent switching would have occurred recently enough to reflect current practice and reveal relevant issues associated with brand switching.

As the indication for lamotrigine use is in epilepsy and bipolar disorder only, the number of patients and size of the data were anticipated to be smaller than for other medicines so as to be manageable, but large enough to test the process. Additionally, lamotrigine sits within a therapeutic class of medicines traditionally considered clinically non-interchangeable regarding switching between brands, the implications of which in part meant that resistance to switching was likely, yet making testing the non-interchangeability hypothesis all the more important.

Once the process had been tested and refined, three further medicines were chosen to include in the study. Although there are more medicines for which similar analysis would be beneficial to both funders and clinicians, only three more medicines could be analysed within the study time frame.

4.4.2. Olanzapine, Risperidone and Venlafaxine

The PHARMAC annual review for the period 2010/11 formed the basis of selection of these further three medicines. At this time, the therapeutic class accounting for the single greatest portion of the annual community pharmaceutical budget was antipsychotic medicines, consuming NZ$60million out of the NZ$706million 2010/11 expenditure.42 Examining the list of individual medicines which accounted for greatest expenditure revealed that olanzapine, risperidone and venlafaxine were in the top 10 medicines by cost funded by PHARMAC in 2010/11.42

In the clinical setting, generic versions of such medicines are likely to be implicitly, if not explicitly, considered non-interchangeable, as is lamotrigine, making them all the more important to investigate. Lessons learned from examining the different mechanisms whereby PHARMAC achieved savings for each of these medicines can be extrapolated to other medicines in the NZ Pharmaceutical Schedule and also more widely by countries watching the lead example of PHARMAC.

Each of these medicines had been targeted by PHARMAC, with generic reference pricing applied to them. Changes to the Schedule-listed brands available for prescription and dispensing had been made. The date of removal or change in funding of the originator brand is hereafter defined as the ‘index date’ for that medicine. Each of the medicines however, had slightly
different funding conditions attached to them, allowing the different funding scenarios to be explored and comparisons drawn between them.

In the case of olanzapine, PHARMAC estimated “that the proposal to apply reference pricing across brands of olanzapine would provide savings to the Pharmaceutical Budget in the region of $30 million per year ($2.5 million per month)”\(^{202}\). The supplier of the originator Zyprexa brand decided to hold their price at the original level, and not to decrease the price to that of the generic brands (a 30-fold difference). PHARMAC in turn, decided not to continue funding the originator brand, and from 1\(^{st}\) September 2011 patients were faced with the choice of switching to a fully funded brand or paying for the originator brand.\(^{203}\)

Similarly, the originator Risperdal brand of risperidone was no longer funded following the introduction of two further generic brands (Dr Reddy’s and Apo-risperidone) in addition to the existing generic Ridal brand.\(^{203}\) However, the Risperdal brand had price protection until July 2012.

In the case of venlafaxine, both the originator brand and the generic equivalent were fully funded, with an agreement in place for the price to decrease over time. A negative incentive thus existed for pharmacists to initiate brand switches as the cost of the originator brand remained higher than the generic and hence the proportional mark-up/return for the pharmacy was greater for the originator brand (since 4% of $17.50 for the Efexor brand is greater than 4% of $6.50 for the generic brand).\(^{203}\) In addition, an agreement from PHARMAC to protect the price of the originator Efexor brand is in place until 2017, together with a confidential ‘bundling’ arrangement for the supply of other medicines from the same pharmaceutical company.

Again, as in the case of lamotrigine, these three medicines are used in conditions in which a cautious approach might be warranted in making any changes that might result in a decrease in therapeutic efficacy. Risperidone and olanzapine are used in patients with a condition in which psychosis is a feature. Such conditions can be socially disabling, yet can be controlled with medication and other forms of therapy. Adherence to therapy is an important feature of therapy in this scenario and anything which threatens adherence should be avoided.\(^{204,205}\) There is no evidence to suggest that a change in brand affects likelihood to adhere.\(^{206}\) However, given that suspicion is a feature of this illness and trust being a prerequisite to successful therapy, differences in appearance (colour, size, packaging) such as those apparent between different brands, have the potential to increase non-adherence and increase total costs of illness.\(^{207}\) Venlafaxine is used as a third-line option when two other antidepressant medicines have been tested and failed to achieve resolution of the condition. Considering the indication for using venlafaxine in this instance is severe, treatment-resistant depression, a similarly cautious approach to changing brand might be expected by the prescriber and patient alike. This is
probably reflected in the implementation of the pricing policy by PHARMAC, who, at least in the case of risperidone and venlafaxine, left the originator brand in the Schedule with a phased decrease in price of originator brand implemented and allowing a passive uptake of the generic brands by new, as well as existing users, of the medicines. In the instance of olanzapine, the suppliers of the originator brand chose not to reduce their price to meet the generic reference price, and the product was delisted from the Schedule.\textsuperscript{12}

### Table 4.1 Key features of the study medicines

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use for which the medicine was funded</td>
<td>Epilepsy, bipolar disorder (and off-licence use in migraine)</td>
<td>Schizophrenia, aggression in dementia</td>
<td>Schizophrenia, aggression in dementia</td>
<td>Resistant depression (3\textsuperscript{rd} line treatment)</td>
</tr>
<tr>
<td>Index date\textsuperscript{1}</td>
<td>February 2007</td>
<td>July 2012</td>
<td>June 2011</td>
<td>September 2011</td>
</tr>
<tr>
<td>Originator brand funding status before index date</td>
<td>Fully funded</td>
<td>Fully funded</td>
<td>Fully funded</td>
<td>Fully funded</td>
</tr>
<tr>
<td>Originator brand funding status after index date</td>
<td>Remains fully funded with Special Authority conditions</td>
<td>Not funded</td>
<td>Not funded</td>
<td>Remains fully funded with Special Authority conditions</td>
</tr>
<tr>
<td>Number of generic versions available and fully funded\textsuperscript{2}</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Study groups</td>
<td>Switchers (originator brand to generic) versus non-switchers</td>
<td>Originator brand switchers versus originator non-switchers and versus generic non-switchers</td>
<td>Originator brand switchers versus same patients one year earlier (no non-switcher patients)</td>
<td>Switchers (originator brand to generic) versus non-switchers for both non-naïve and new users</td>
</tr>
</tbody>
</table>

\textsuperscript{1} The Index date is the date upon which the reference pricing policy for that medicine became effective.

\textsuperscript{2} During the study periods

### 4.5. Identifying the study patients

#### 4.5.1. The National Health Index number and associated codes

Every New Zealander has a national health index number (NHI) assigned to them, either at birth or at first contact with the healthcare system, and a national database of all NHI numbers exists. All pharmacy and general practitioner record systems use this NHI number, as do all the national health collections maintained by the New Zealand Health Information Service (NZHIS). The NHI is linked to a patient’s name, date of birth, gender, ethnicity, domicile (census area unit) and a deprivation index score, and is unique to a patient. A study in 2004 evaluated the linkage of databases through an encrypted NHI, finding 99.6% matching for date of birth between NHI at the GP and national admissions data, 99.1% for gender and 84% for ethnicity, and concluded that the use of databases for healthcare research linked in such a manner was valid.\textsuperscript{208}
Ethnicity codes are defined by the NZHIS and contain 3 levels. The primary level contains six categories (European, Māori, Pacific peoples, Asian, Middle Eastern/Latin American/African and ‘other’, whereas level 2 codes distinguish between these levels. ‘Pacific peoples’ is further defined as Samoan, Cook Island Māori, Tongan, Niuean, Tokelauan or Fijian ethnicities, and ‘Asians’ as Southeast Asian, Chinese, Indian, or ‘Asian not further defined’. Studies have examined the specificity of ethnicity coding and report some weakness in assigning level 2 codes, but not at level 1. This study used level 1 codes only.

The New Zealand small-area index of relative socio-economic deprivation (‘NZDep’), was developed to highlight disparity and aid in resource allocation and priority setting in policymaking, and was derived in part based on the Canadian National Occupancy formula and similar Organisation for Economic Cooperation and Development (OECD) formula for crowding. The NZDep is a composite score from variables of access to car and telephone, receipt of means-tested benefits, unemployment, household income, sole parenting, educational qualifications, home ownership and home living space. An index of 10 indicates the area of domicile contains the most socially and materially deprived scores, whilst that of 1 applies to an area of highest wealth. Widely used in health research, as well as by planners and for the allocation of health funds in New Zealand, it should be noted that the NZDep, associated with an individual’s home address, is an area measure rather than an individual’s score. Some inaccuracy may exist in the association of a patient’s address in the national health collections with the NZDep score due to an observed increased mobility of people living in the most deprived areas. However, following the implementation of capitation-based payments to primary health organisations for enrolled patients in 2001, accuracy of patient addresses and thus NZDep is likely to be higher.

4.5.2. The Pharmaceutical Collection database

Records of all prescriptions dispensed in NZ are recorded in the national ‘Pharmaceutical Collection’, a database housed by the Ministry of Health. It is this database which was used to identify all patients taking the four study medicines and to then select patients to be included in the study. The following sections describe the database and the method of identifying patients.

The national ‘Pharmaceutical Collection’ or ‘PHARMS’ database consists of all claims and payment information for all subsidised dispensings within NZ, and contains data from 1 July 1992 to date. It is updated on a fortnightly basis when claims for reimbursement are made by the dispensing pharmacies.

All prescription items within the PHARMS dataset are coded with a unique ‘Pharmacode’ describing the item with dimensions that include both the manufacturer’s name and the official chemical name, the formulation (e.g. tablet, oro-dispersible wafer, suspension, injection, or
suppository), and the strength as well as the dose, quantity dispensed and date of dispensing. Since 1998, all prescription items in the dataset were coded using the pharmacy stock code (the ‘Pharmacode’) prior to which a different coding system was in place. These codes are logically maintained by PHARMAC which is responsible for the negotiations with companies which lead to the listing of individual product items in the Schedule. It is the specific Pharmacode which allows the database to be used to identify patients who have been dispensed the originator brand of a medicine and those who have received a generic brand.

Each dispensed item is associated with the name, age, gender, and unique National Health Index number (NHI) of the patient. Special codes are used to identify certain endorsements or permissions required for the item to be legally dispensed, such as authority from a specialist, or from PHARMAC. Other variables are also embedded in the dataset such as the identity of the prescriber and the pharmacy at which it was dispensed.

Permission to access anonymised data (in the form of an encrypted NHI number and removal of the patient name attribute) was obtained from the Ministry of Health and from PHARMAC, and specifications for the extraction of data were developed together with data analysts from the National Health Board.

4.5.3. Using the index date to select patients

The date upon which a new medicine brand becomes the preferred brand listed in the Schedule is advertised to pharmacies and medical practices months in advance. The subsidy conditions of all brands of that particular chemical entity are also detailed in the Schedule and other communications from PHARMAC. This keeps prescribers informed of pending brand changes and enables pharmacies to run down stocks of the previous brand whilst ensuring they have stocks of the new brand on the relevant date.

The index dates (being the date on which the change in funding occurs for a particular medicine) and funding conditions for the four study medicines are detailed in table 4.1 (above).

The steps taken to identify the study groups are described below, together with an explanation or rationale for each step. The specific data extraction periods and patient characteristics for each study medicine is described within the case report for each medicine in the chapter on study findings in this thesis; see Chapter 5.

Step 1. Identify all relevant Pharmacodes by brand name and preparation form and strength.
As a maximum of 3-month’s supply of medicines can be dispensed at a time, a 3-month period following the index date was used to identify all patients (by their unique NHI) taking the study medicine during that time.

Step 2. Search PHARMS database for all dispensing records of these Pharmacodes between the index date and the subsequent 3-months. Identify all NHI numbers associated with these dispensing records. Extract all dispensing records for all medicines for these NHI numbers.

Depending on the individual study medicine criteria, patients were included if dispensing records existed for 5 out of 6 months or 11 out of 12 months for the period prior to the index date, i.e. they had been taking the study medicine continuously for at least 6 months or a year prior to a change in the Schedule-listed brand occurring. A one-year period was chosen for lamotrigine as an indication of the patient being stable on lamotrigine treatment, although it is acknowledged that a dispensing record does not necessarily mean that the patient is treatment-adherent (see Limitations, section 4.6.1). For the remaining 3 medicines, patients needed to be taking the medicine for 6 months to be included. Patients not meeting these criteria were excluded from the analysis.

Step 3. For all the extracted NHI numbers, confirm that continuous (either 5 out of 6 months or 11 of 12 months) dispensings records exist. Remove dispensing records for NHI numbers not meeting this criteria.

The brand specific ‘Pharmacode’ in the PHARMS dataset was used to identify the first date a different brand was dispensed.

Step 4. Using product specific Pharmacodes, for each unique NHI, identify the first instance a different brand of the study medicine is dispensed. The date on which this occurs is the ‘switch date’.

For this study, a ‘switcher’ is defined as a patient who continuously uses the first study medicine brand and then switches to a second brand within 365 days from the index date. Patients who switched back to the first brand at any time, or who made further switches to other brands, are still deemed ‘switchers’. In the same context, a ‘non-switcher’ does not make a change in brand at any time within one year of the index date.

Step 5. For all patients whose switch date occurs within 365 days of the index date, assign the status as ‘switcher’. For all patients where a change in brand does not occur either within a year of the index date, or at all, assign a ‘non-switcher’ status.

Step 6. In the case of olanzapine, only 16 patients did not switch to a generic brand, and their dispensing records were removed from the working dataset. All included ‘switcher’
patients were used as their own controls, using a ‘no-intervention’ period one year before their individual switch dates. (See Figure x. Chapter5: Findings).

**Patient demographics and Explanatory variables**

Demographics collected for the groups included age, gender, ethnicity and level of socio-economic deprivation of domicile (‘NZDep’). These demographics exist in both the PHARMS database as well as in the other national health data collections and were used to validate the extraction of data using the encrypted NHI numbers.

**Co-morbidity (multi-disease) scores**

Prescription records were used to identify baseline comorbidities. Different systems for scoring comorbidities have been described; however, reviews of the scoring systems note that there is no one system that is better than the others, no accepted ‘gold standard’. The systems have been developed to fulfil different purposes and are based on specific but differing populations, and as such may be less or more sensitive/ specific.

Most of the systems use ICD-9 or other diagnostic codes, whilst a few use medications as the primary source of information-the so called Chronic Disease Score (CDS). The basic construct is the more diseases a person has, the worse off they are and the more resources they will consume and hence the index is disease-based. The chronic disease score converts prescribed medicines into disease groups and then uses this information to inform costs or outcomes – with or without additional weighting for the relative severity of the disease. Schneeweis (2001) and Perkins (2004) both suggest a simplified score of the number of distinct prescription medicines over a baseline period (one year) is as effective in predicting future healthcare utilisation as using a weighted CDS, whilst Hazlet (2002) uses mean prescriptions per month as an outcome variable that may be influenced by the reference-pricing intervention alongside of other transactions at a visit to the doctor.

**Table 4.2: Summary of patient attributes**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study age</td>
<td>Age in years as at the index date</td>
</tr>
<tr>
<td>Gender</td>
<td>Male or female</td>
</tr>
<tr>
<td>European ethnicity</td>
<td>Level 1 ethnicity codes used by the Ministry of Health (and consistent with national census data)</td>
</tr>
<tr>
<td>Māori or Pacific peoples ethnicity</td>
<td></td>
</tr>
<tr>
<td>Living in area of high socio-economic deprivation (NZDep 7 – 10)</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Comorbidity score</td>
<td>Count of all unique medicines used in chronic disease over one year</td>
</tr>
<tr>
<td>No. of unique (acute and chronic) prescription medicines</td>
<td>Count</td>
</tr>
</tbody>
</table>
This study used an unweighted chronic disease score, using the World Health Organization’s Anatomical Therapeutic Chemical (ATC) classification system for all unique chronic medicines (excluding the therapeutic class of the study medicine) dispensed to each patient. 223

4.6. Medicine-related outcome variables

A summary of all medicine-related variables is given in Table 4.3 below, whilst the computation of each variable is described in more detail in this section.

*Time to switch, Switch-back & Switch Count*

Individualised ‘time to switch’ for patients was calculated as the difference between the switch and index dates; for non-switchers there is thus no ‘time to switch’ variable. Additional switching variables analysed include the incidence of patients switching back to the originator brand and similarly the incidence of making a single switch and a count of the number of switches made.

All prescription records for the included cohorts were extracted from the PHARMS database for a one-year period before and after the individual switch or index dates. In the case of venlafaxine only, a refinement was made whereby, rather than the index date being set to the policy intervention date for non-switchers, non-switchers were randomly assigned an index date using the switch dates of the switchers. Thus a matching proportion of switch/index dates was attained between the switcher and non-switcher groups, with a likely increase in specificity of comparator periods for outcome measurements.

*Change in dosage*

Where the information existed in the PHARMS data, records were examined for a change in dose of the study medicine in the 6-month period before and after the switch/index date, as an indication of change in therapeutic response to the medicine.

*Concomitant medication*

Medicines in the PHARMS database are coded according to the World Health Organization’s Anatomical Therapeutic Chemical (ATC) Classification System. The ATC classification has five levels, the 5th of which is the chemical substance of the medicine itself. The first level of the code indicates the anatomical main group such as nervous system (all four study medicines) or, for example cardiovascular system. The second and 3rd levels (TG2 and TG3) indicate diseases or conditions which the medicine is used in, i.e. the therapeutic grouping.
The TG2 level “N03” is for all antiepileptic medicines, whilst lamotrigine is found in the TG3 grouping of “N03AX: other antiepileptics” as it is a newer and non-typical antiepileptic medicine. The antipsychotic risperidone and olanzapine medicines are grouped at the level of TG3 and being psycholeptic medicines (TG2). Venlafaxine is an antidepressant medicine (TG3) of the psychoanaleptic TG2 group.

Using these therapeutic group codes in the PHARMS database, a count of concomitant medicines used specifically to treat the primary indication was made (reported as percentage of patients on monotherapy), and any change in the number of medicines 6 months post-switch/index dates noted. In the case of risperidone and olanzapine any change in the annual use of injectable antipsychotic medicines was also used as a measure of change in the patients’ condition, whereby a need for injectable therapy, rather than oral, indicates an exacerbation or worsening of their condition.

Unique prescription medicines per year

The PHARMS dataset was then used to count the number of unique prescription medicines in the year (to minimise seasonal effects) before and after the switch or index date. This indicator was used for its potential to highlight side effects such as, for example, nausea or gastrointestinal reflux which might then result in the addition of a new medicine to manage that side effect. In addition, it is a supplemental indicator of a change in the patient’s overall health status.

Table 4.3: Summary of medicine-related variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to switch</td>
<td>Days from index date to date on which first change in brand occurs</td>
</tr>
<tr>
<td>Number of switches made</td>
<td>Count (irrespective of type: originator to generic, generic to originator, generic to generic)</td>
</tr>
<tr>
<td>Incidence of switch-back</td>
<td>Proportion of switchers who switch back to originator brand before the next expected dispensing (generally before 28 days)</td>
</tr>
<tr>
<td>Change in total daily dose</td>
<td>Difference</td>
</tr>
<tr>
<td>Change in concomitant TG3 medicines</td>
<td>Difference in count of medicines at therapeutic group level 3</td>
</tr>
<tr>
<td>Use of injectable antipsychotic medicine</td>
<td>Count (using specific Pharmacode)</td>
</tr>
<tr>
<td>Change in annual number of unique prescription medicines</td>
<td>Difference in count of unique prescription medicines over one year after minus before index date</td>
</tr>
<tr>
<td>Count of ADR reported</td>
<td>Count of reports from CARM data</td>
</tr>
</tbody>
</table>

Adverse event reporting

The incidence of sentinel reports of adverse events for the study medicines was obtained for each study medicine from New Zealand’s national Centre for Adverse Reactions Monitoring in Dunedin (CARM). CARM receives ad hoc reports usually only from medical practitioners, but on occasion from patients and the pharmaceutical industry. Data were available as annual
counts of reports received, and these were further divided into those reports related, and those unrelated, to a brand-switch. Further patient detail was not available, nor which specific brand was involved in the case of brand-switch related reports.

4.6.1. Limitations of the PHARMS dataset

Validity of NHI numbers

This study relies on the NHI number for patient identification in the first instance; secondly an accurate NHI is required to link all other prescription items dispensed to the same patient over time, and thirdly to link and identify individual patient events in all the other health databases. Prior to 2007, rates for completion of NHIs were reportedly low, with estimates in the order of 72–88 % completeness. The PHARMS dataset theoretically suffers less from this deficiency, as the system within the dispensary checks the NHI number being manually entered by the pharmacist and rejects invalid NHI numbers. Pharmacies now have the ability to look up NHI numbers in a national database via a secure internet site.

The PHARMAC requirement for patient-based special authority (SA) approval to fund specific medicines adds both to the likelihood that the NHI is correctly applied and to the percentage of completeness. Except in the case of risperidone, the patients using the medicines used as exemplars in this study required an SA number for funding, without which patients would have had to pay the full cost of the medicine. Procedurally, the awarding of an SA number by PHARMAC requires submission of an application per patient by the prescribing doctor, including the patient’s NHI. This process in turn further enhances the accuracy and completeness of NHI numbers.

Additionally, as the PHARMS collection is used to make reimbursement payments to pharmacies, pharmacy managers have a direct interest in the correct coding of patients. The portion of co-payment made by the patient at the time of collection of their medicines varies per patient and is deducted before reimbursement by the Ministry of Health. Completeness of NHI numbers is thus less of an issue, whereas incorrect or multiple NHI numbers for a patient probably still persists.

All of the datasets used in this study contained patient age, gender and area of domicile attributes as well as an encrypted NHI number. This allowed a further check to be made of the likelihood of the patient identified in the PHARMS dataset being the same patient identified in the other health collections. Any PHARMS data with missing NHI numbers were removed from the dataset; this ranged from 2.8% to 6.1% of total prescription items.
Lack of Diagnosis

For historical and privacy reasons, there is no requirement for a diagnosis with regard to dispensing a medicine, or for the reimbursements made to the pharmacies via the PHARMS database. This is despite medicines being listed in the Schedule for disease- or condition–specific causes. Any prescribing that is for non-approved conditions is termed “off-label” prescribing. In the case of lamotrigine, it is thus impossible to determine with accuracy if the medicine is being prescribed as an antiepileptic medicine or for migraine or bipolar disorder. Likewise, a lack of diagnosis means that it is unclear if risperidone or olanzapine are being used for schizophrenia or behavioural and psychological symptoms in dementia or other mood disorders, or anxiety. Examining concomitant medicines and patient age can only help to some degree in identifying likely diagnoses. However, the limitation of a lack of diagnosis is muted to some extent as all the study medicines are used in chronic conditions reducing the relevance of diagnosis.

No data on Adherence to treatment

Pharmacy databases are generally recognised as an approximation of medicine use, however, the dispensing of a medicine does not equate to actual use, nor will the database record those prescriptions which are not dispensed. Although the methodology does not allow follow-up at patient level to determine adherence, dispensing records exist for all of the patients beyond the switch date, suggesting continued consumption of the medication and minimal impact of switching on adherence.

Inadequate Dosage data

Data fields captured in the PHARMS database include dosage strength, frequency and total quantity dispensed – enabling a computation of total daily dosage. However, in the dispensary systems within the dispensary which provide the data for the PHARMS dataset, only the strength and quantity fields have strict valid integers allowed, whereas the frequency variable is embedded within the dosage instruction field and can be overridden. Once extracted from the dispensary system and delivered into the PHARMS database the frequency field may be empty or have other information in it which makes calculating a daily dosage impossible for that record. Dosages were calculated for the study medicines where possible and are reported in the findings.

Data on unfunded medicines

The PHARMS dataset is used primarily for administrative purposes, rather than for clinical or research purposes: it is the basis upon which pharmacies make claims for reimbursement to the DHB. Records of medicines which have been dispensed, but which are not listed in the
Schedule, and thus not funded, are not housed in the PHARMS data. For example, sildenafil, outside of use in pulmonary arterial hypertension, is an unfunded prescription medicine, the dispensing of which will be recorded within each pharmacy dispensary record, but will not be retained within the PHARMS dataset.

All brands of the medicines studied in this thesis were either funded in full, or in part, or had SA numbers associated with them, and as such, instances of dispensings could be retrieved from the dataset. Likewise, there were no medicines prescribed for the same indications as the study medicines (epilepsy, bipolar disorder, migraine or mental health conditions) which were unfunded or not listed in the Schedule.

4.7. Extracting Health Service Use data for the cohorts

The National Minimum Dataset (NMDS) is a national collection of hospital discharge information, including coded clinical data for inpatients and day patients, whilst the National Non-Admitted Patients Collection (NNPAC) information includes event-based purchase units of medical and surgical outpatient events and visits to the emergency department. The Mortality Collection records the underlying cause of death for all deaths registered in New Zealand. These collections were used to identify contacts made within the health sector by all the included patients.

Using the Ministry of Health data dictionaries, codes which reflected either follow-up visits or pre-admission contacts were removed from the NNPAC dataset, leaving those contacts with specialist outpatient services which were the first visit of community or other service referrals. Similarly, admissions in the NMDS which were coded ‘intended day-case’ were removed, leaving only acute admission-type contacts in the dataset.

4.7.1. All-cause versus disease-specific coding

Initially, only records in these datasets which contained the diagnostic codes related to the disease for which the study medicine might be used, were selected. For example, lamotrigine is an antiepileptic and mental health and behavioural medicine and so records with ICD codes related to epilepsy and seizures were retained, as well as ICD codes for medicine overdose, medicine-related adverse effects, amongst others. However, this was later widened to retain all causes for admissions and visits to outpatient services for the following reasons. Firstly, too few disease-specific events remained in the dataset using these narrow, focused ICD codes, resulting in wide-confidence limits when statistical comparisons were made between study groups. Secondly, consequences of a change in therapeutic response might not be limited to a single specific event type, and hence a single and specific admission cause. For example, a
change in therapeutic control of epilepsy might well result in a seizure; however, the cause of admission to the emergency department might be due to injuries sustained as a result of a motor vehicle accident which in turn may have been due to having a seizure, all of which may or may not have been captured accurately in the admission data. This scenario also describes the final reason for retaining all-cause related contacts with the health services: that of inaccuracies in patient record coding.

The Mortality Collection was examined to identify any of the study participants. Relating a change in brand to cause of death could not realistically be undertaken. Up to seven cause fields were extracted from the collection; however, many were coded “Subject to Coroner’s finding”, and distinguishing between the primary cause of death and underlying conditions contributing to death could not be made with any certainty. Again, all-cause mortality was thus used as the variable.

Data were thus extracted from the NMDS, NNPAC and mortality collections for any cause for all included patients selected from the PHARMS dataset.

4.8. Health services use Outcome variables

Encounters with the health system, at an emergency department, outpatient specialist clinics and hospitalisations at individual patient level were counted for 30 days, 6 months or 1 year before and after switch or index dates for switcher and non-switcher groups respectively. Differences in the number of health events for both the pre- and post-index periods were used to determine the change in rate of utilisation, and statistical difference-in-differences was examined. The specific hospital service data extraction periods for each study medicine is described within the case report in the chapter on study findings in this thesis; see Chapter 5.

Deaths were identified for up to one year after the switch or index date, and reported as a rate for each group.

Table 4.4: Summary of health outcome variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of the Emergency Dept. (ED)</td>
<td>Count of any events over defined period of time (7 or 30 days, 6 or 12 months), before and after index date</td>
</tr>
<tr>
<td>Use of specialist outpatient services</td>
<td>Count of any events, except follow-up visits, over defined period of time (6 or 12 months), before and after index date</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>Count of all hospital admissions, except planned admissions, before and after index date</td>
</tr>
<tr>
<td>Death</td>
<td>Death occurring within 365 days of the study index date</td>
</tr>
</tbody>
</table>
4.8.1. Limitations of the NZ National Health Collection datasets

Inaccuracies in coding and in the NHI number itself have been described above in the limitations of the PHARMS database, and apply as much, if not more so in these databases which are used primarily for administrative reasons, unlike the payments-based PHARMS collection.

Data within these collections are primarily focused on services provided at the hospital interface, and do not capture community based services, including visits to the general practitioner, or contacts with the network of the community mental health team, case managers and other support workers. Evaluating the use of these services would be a better measure of adverse outcomes of brand switching than at secondary level of care; however, the data were not collected during the study periods due to a change in funding of services provided by PHOs. This is a major limitation as any change in administrative or cost burden at the community level cannot be measured. Similarly, any additional pharmacy usage by patients cannot be measured using the national databases, nor events which are self-managed by the patients themselves.

4.9. Chapter Summary

This thesis can be viewed as a two-part, two-method study with each part complementing the other. Part 1 evaluates the effects of reference pricing for four medicines using a retrospective observational difference-in-differences design, the methodology of which has been described in this chapter. (The rationale and methodology for Part 2 are described in Chapter 6.)

The rationale for selecting the four exemplar medicines – lamotrigine, risperidone, olanzapine and venlafaxine - has been described, and the data extraction process detailed. The outcome measures have been defined as they were used in the four case studies, allowing for comparisons amongst all four to be made, and potentially also with other studies. Limitations of New Zealand’s national datasets have been highlighted, especially the lack of data from primary or community level.

The next chapter presents the findings for each case study, together with specific detail for each study medicine, in the form in which they were published in peer-reviewed journals. An examination of themes that emerged from examining all four medicines together is also presented.
Chapter 5. Findings Part 1: the case studies

The previous chapter described the overall methodology used in evaluating data for Part 1 of this research. The case studies of all four study medicines – lamotrigine, risperidone, olanzapine and venlafaxine – have been published in peer-reviewed journals, and the findings are reproduced in this chapter with permission. For each medicine, only that information which clarifies the individual medicine and study parameters has been retained from the original published “Introduction” and “Methods” sections.

The citations for the four articles are listed below.

5.1. Lamotrigine

5.1.1. Introduction

Lamotrigine is an example of a newer anti-epileptic medicine which was introduced into New Zealand in 1994 as a second-line agent in the management of epilepsy, restricted in the PHARMAC Schedule (via a “Special Authority” arrangement) for use in patients not adequately managed with at least two other anti-epileptic medicines.225

Specific arguments against generic substitution of anti-epileptic medicines centre on the concept of a narrow therapeutic index, whereby small changes in serum concentration of a medicine could theoretically result in loss of therapeutic efficacy, or in toxicity. Loss of efficacy in a condition such as epilepsy has profound social consequences alongside medical and financial costs, especially when a patient has been seizure-free for a period of time, and a reluctance to change between brands is thus understandable.

Clear evidence on the (non-)interchangeability of anti-epileptic medicines is however lacking, as is clarity from regulatory and professional authorities on the issue.226-229 The American Academy of Neurology, opposes generic substitution of all anti-epileptic medicines without physician and patient approval,95 although this 2006 guideline is under review; whilst in Canada, the province of Ontario mandates generic substitution of all lamotrigine prescriptions.112 In the UK, the National Institute for Health and Care Excellence (NICE), in contradiction to guidance from the Scottish Intercollegiate Guidelines Network (SIGN), advises caution with regard to carbamazepine and phenytoin only, all other anti-epileptic medicines being considered interchangeable.230 Prospective comparative studies evaluating outcomes of switching between brand and generic anti-epileptic medicines, to advise such position statements, are generally lacking. Those that are available in the literature were primarily conducted in the 1990s, are limited predominantly to carbamazepine and frequently (14 out of 20 studies included in a systematic review231) funded by pharmaceutical companies.232,140

NZ Policy on funding for lamotrigine

The agreed subsidy for 56 tablets of 100mg originator brand Lamictal® was NZ$150.213 In 2003, generic versions of lamotrigine arrived in the international marketplace,112 and on the 1st February 2007 two generic lamotrigine preparations with agreed subsidies of approximately NZ$75 for the same quantity and strength were used to reference-price the originator lamotrigine brand. The originator brand continued to be subsidised at NZ$150 until 1st July 2007, after which its agreed price decreased to NZ$80.234 With a reduction in cost, access to lamotrigine was widened to include patients newly diagnosed with epilepsy and for use in
patients with depressive episodes in bipolar disorder. Special Authority approval was no longer required for lamotrigine after reference pricing and the introduction of generic lamotrigine, and prescriptions for Lamictal® continue to be fully subsidised. In 2008 a third generic lamotrigine product was introduced, with a subsequent decrease in price of the existing generic products to match it (NZ$60). However, the originator brand remained at NZ$80 with the price differential between originator and generic thus increasing from 6% in 2007 to 33%. Currently, in 2013 there are 4 lamotrigine preparations listed for full subsidy in the Schedule, the fourth product at an agreed price of $NZ57.

Study parameters

The study group comprised all adults (from 14 years of age onwards) for whom lamotrigine had been dispensed at least once during each quarter in the study year 01 February 2006 to 01 February 2007, the latter being the study index date on which the generic brands became available for prescription and access widened.

5.1.2. Results

Demographics of the cohorts

1655 adult patients were included in the study cohort having been dispensed lamotrigine for at least one year prior to the study index date, 01 February 2007. Of these, 361 patients (21.8%) switched from originator lamotrigine to a generic equivalent (herein after called ‘switchers’), whilst the remaining 1298 stayed on the originator brand throughout (and hence formed the ‘non-switcher’ group). Table 5.1.1 shows the demographic characteristics of the groups.

Significant differences existed between the groups with more male, Māori or Pacifica switchers than non-switchers; however, the correlation between variables and allocation to switching/non-switching group was low, accounting for less than 1% of the variance. Switchers also had a slightly higher mean comorbidity score; the unique prescription medicine count for switchers was not significantly different from non-switchers. The correlation between the demographic variables and switching was examined (see Table 5.1.1); however, correlations were low and a lack of confounding was confirmed by an analysis of covariance. Consequently, the analysis of outcomes was not adjusted for these variables.
Table 5.1.1: Demographics and baseline measures of lamotrigine non-switchers and switchers

<table>
<thead>
<tr>
<th>Measure</th>
<th>Non-switchers* (n=1298)</th>
<th>Switchers* (n = 361)</th>
<th>Significance (p value); Correlation# (Pearson’s r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>40.2</td>
<td>41.2</td>
<td>0.304</td>
</tr>
<tr>
<td>Female (%)</td>
<td>55.5</td>
<td>46.3</td>
<td>0.002; (0.08)</td>
</tr>
<tr>
<td>European (%)</td>
<td>81.4</td>
<td>77.8</td>
<td>0.153</td>
</tr>
<tr>
<td>Māori or Pacific Peoples (%)</td>
<td>12.9</td>
<td>18.8</td>
<td>0.006; (0.07)</td>
</tr>
<tr>
<td>NZDep of 1-4# (least deprived) (%)</td>
<td>34.4</td>
<td>32.5</td>
<td>0.53</td>
</tr>
<tr>
<td>NZDep of 7-10# (most deprived) (%)</td>
<td>43.6</td>
<td>49.2</td>
<td>0.063; (0.05)</td>
</tr>
<tr>
<td>Comorbidity Score (mean)</td>
<td>1.15</td>
<td>1.24</td>
<td>0.042; (0.05)</td>
</tr>
<tr>
<td>No. of unique prescription medicines pre-index (mean)</td>
<td>6.45</td>
<td>7.01</td>
<td>0.141</td>
</tr>
<tr>
<td>Lamotrigine as monotherapy (%)</td>
<td>25.5</td>
<td>22.4</td>
<td>0.242</td>
</tr>
<tr>
<td>Patients receiving concomitant antipsychotic therapy pre-index (%)</td>
<td>7</td>
<td>9</td>
<td>0.364</td>
</tr>
</tbody>
</table>

NZDep: New Zealand index of relative socio-economic deprivation

*Switcher = Patient changing from originator brand to generic equivalent following implementation of generic reference pricing of lamotrigine on 01 February 2007. Non-switchers did not make a change in brand.

# Correlation of baseline measure with switching to generic lamotrigine

Switch behaviour

Amongst the switchers, 60% made a single switch to a generic product with no further switches to any other brand throughout the study period. Approximately 30% made one further switch only (either generic to generic, or generic to originator), with the remaining 10% making 3 or more successive switches. One patient made as many as 3 switches within a 6 month period and four patients made at least 5 switches within 13 months.

Time to first switch: The maximum period supply of lamotrigine is 30 days, with few patients (n=41) receiving weekly or fortnightly dispensings. Hence the first opportunity for most patients to switch from originator to generic would be expected to lie within 30 days from their last dispensing. The mean time to switch for all switchers was 163 days (range 7-365 days). Few switchers (7.5%) changed to a generic within their first refill opportunity (being the first 30 +/- 7 days from their last dispensing). Of patients regularly receiving a 90-day prescription from their doctor 35% switched brands before dispensing commenced against a new prescription.

Switch-back rate: Approximately one quarter of switchers ultimately switched back to the originator brand. 3% of these switch-backs occurred within 30 days of the first switch, with a mean time to switch-back of 16 days (min 4 days, max 28 days). Within a 60-day period, approximately 8% had switched back to the originator brand, and just over 1% of patients changed on to a second generic product.
Health outcomes

The findings for health outcomes observed amongst switchers and non-switchers are summarised in Table 5.1.2.

Emergency department (ED): An increase of 0.21 visits to the ED was found in non-switchers (p=0.000) 1 year after the index date, whilst for switchers the mean difference was not significant. There was no significant difference between switchers and non-switchers in the mean change in number of visits to the ED from the year before the index or switch date and one year post.

Hospital admissions: No significant differences were found for all hospital admission variables. Rates of admissions were 46 visits/100 persons for switchers both pre- and post-switch, and 34/100 and 31/100 for non-switchers pre- and post-index date respectively.

Use of a specialist service: There was no significant difference between switchers and non-switchers in the mean change in use of outpatient specialist services from the year before the index or switch date and one year post.

Death: The number of deaths amongst study patients was low, with 11 deaths in the non-switcher group and 3 amongst switchers (both groups 0.8%). This is slightly higher than the national death rate for 2007 of 0.67 per 100 residents. Two of the deaths in the non-switcher group were recorded as related to epilepsy; however the numbers are too small to attribute causality.

Use of other anti-epileptic medicines

The mean difference in the number of anti-epileptic medicines used after the index date was compared with the one year period before. Both switchers and non-switchers had non-significant changes in the use of anti-epileptic medicines. The difference of the means between groups was not significant either.

Reports to CARM

Reports of adverse events from doctors in the main, but also from pharmacists, patients and the pharmaceutical industry are made to New Zealand’s national Centre for Adverse Reactions Monitoring (CARM). During the period 01Feb 2005 to 01 Feb 2008, 4 case reports related to lamotrigine were received by CARM. All occurred within the one year post-index period (2 cases were reported in June and one each in August and October 2007) and all were related to changes from the originator brand to a generic product. Two of these reports describe loss of therapeutic effect. The other two relate to gastrointestinal symptoms (reflux, abdominal
cramp), blurred vision and dizziness (symptoms for which the originator manufacturer’s data sheet gives an adverse event rate of 1 in 10).  

Table 5.1.2: Health outcomes for lamotrigine non-switchers and switchers

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Non-switchers*</th>
<th>Switchers*</th>
<th>Difference-in-differences (95% CI)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in mean annual visits to the ED per person</td>
<td>0.21</td>
<td>0.17</td>
<td>0.03 (95% CI -0.045 to 0.12)</td>
<td>0.66</td>
</tr>
<tr>
<td>Change in mean annual number of hospital admissions per person</td>
<td>-0.03</td>
<td>0.00</td>
<td>0.03 (95% CI -0.108 to 0.168)</td>
<td>0.67</td>
</tr>
<tr>
<td>Change in mean annual use of specialist outpatient services (visits per person)</td>
<td>-0.35</td>
<td>-0.37</td>
<td>-0.025 (95% CI -0.06 to 0.01)</td>
<td>0.50</td>
</tr>
<tr>
<td>Change in mean annual number of anti-epileptic medicines per person</td>
<td>-0.003</td>
<td>0.03</td>
<td>-0.03 (95% CI -0.16 to 0.10)</td>
<td>0.35</td>
</tr>
<tr>
<td>Deaths (per 100) up to one year after the index date</td>
<td>0.75</td>
<td>0.67</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CI Confidence interval, ED Emergency department

*Switcher = Patient changing from originator brand to generic equivalent following implementation of generic reference pricing of lamotrigine on 01 February 2007. Non-switchers did not make a change in brand.

Healthcare costs:

As no significant differences were found in healthcare utilisation between switchers and non-switchers, there would be no difference in healthcare costs. Therefore no attempt was made to estimate healthcare costs.

5.1.3. Discussion

In the absence of mandatory switching or incentives to change to a less expensive product, the proportion of patients who switched was low (21.8%). Of those patients who did switch, more than 60% did so successfully and remained taking the same version of generic lamotrigine to which they switched.

No significant difference was found between switchers and non-switchers for any of the health outcome measures (ED visits, hospitalisations, referrals to specialist, death or use of adjunctive anti-epileptic medicines). Other similar studies have reported equivocal findings. In a study conducted in the US, no increase in ED visits or hospitalisations was found for patients switching to generic lamotrigine.  

Similarly an event rate ratio of 0.97 (95%CI 0.80 to 1.17) favouring switching, was reported in another US study.  

A higher utilisation of medical services in Quebec (including hospital, emergency department, medical clinics and family medicine groups) was reported amongst switchers (8.7 for non-switchers versus 9.8 visits per person-years for switchers p<0.0001), and a study evaluating all anti-epileptic medicines together (for which lamotrigine accounted for 3% of cases) found an increased odds ratio (1.92 [95%CI1.39 to 2.69]) for switching versus non-switching.
cases (2.64)] of switching in the 6 months prior to an event. However other factors may be relevant with regard to apparent increased use of health services on switching. For example, Gagne et al. investigated the risk of seizure-related events associated with prescriptions refills and switching between brand and generic antiepileptic medicines in Canada. They observed increased odds of a seizure-related event around the time of prescription refill compared to seizure related events between prescription refills, independent of whether or not the refill involved a change in brands. Switching from brand to generic in itself did not appear to be associated with an increase in risk for seizure-related events. Similarly, Hansen et al., using US data, suggest the observed modestly increased odds of a seizure-related event with switching (adjusted odds ratio of 1.27 [95%CI 1.14 to 1.41]), was irrespective of the medication or type of switch (originator to generic, generic to originator, generic to generic).

Four case reports of adverse events were received by CARM. Data received by CARM are housed separately from the NZHIS. As the key National Health Index for all data from NZHIS was received encrypted and that from CARM is anonymised, it is not strictly possible to allocate the 4 cases to either study group. However, as all the cases related to brand-switching and were all in the study time period it is possible they related to ‘switchers’, but could also have been recent lamotrigine users (i.e. they might not have been stable on lamotrigine for a year as the study inclusion criteria required). Assuming they were all switchers gives an event rate of 4 cases per 361 switchers. For the 4 individuals this would be very important, but the difference is statistically non-significant. The incidence of case reports in New Zealand mirrors the low reporting rate in international literature; for example a retrospective review found 14 Health Canada adverse-reaction forms were submitted by pharmacists in Ontario during 2003/04 with regard to brand switching of lamotrigine.

The rate of switch-back in this study (~8% within the first 60 days, and one quarter over the entire study period) was similar to that reported in Canadian studies. A study in Ontario found a switchback rate for lamotrigine of 12.9%, whilst another found a 27.5% switchback for lamotrigine in Quebec, being 3 to 4-fold higher than rates of switchback for comparator medicines. However, a more precise value for switch-back using a time limit of within the first 30 days following dispensing, suggests the proportion of patients for whom the generic lamotrigine was unsuitable for whatever reason (3% in this study) is more in tune with values expected for any change in brand for any medicine, and this is further supported by the relative lack of adverse reports made to the national reporting centre for adverse events CARM.

Three or more successive switches were made by approximately 10% of the switcher group. Some researchers suggest generic to generic switching should be avoided. However evidence to support this notion is lacking, as is the argument that generic medicines differ widely
from their originator counterparts. A study comparing generic and originator medicines over 12 years using bioequivalence data from the FDA found that almost 98% of all bioequivalence studies showed a variation by the generics of less than 10% of the originator area under the curve (AUC) with an average AUC difference of 3.56%, and the average difference in maximum plasma concentration (Cmax) between generic and originator was 4.35%. Variation in bioavailability within different batches of the same originator brand is also recorded by the parent manufacturer.\textsuperscript{244,247} A study in Australia found elevated lamotrigine serum levels associated with stable dosing and continued use of only the originator Lamictal\textsuperscript{®} product. Variation in the site of manufacturer was confirmed by the manufacturer.\textsuperscript{248} Median serum levels of lamotrigine were similar amongst Danish patients who switched between originator and generic lamotrigine brands and those who did not switch in one study,\textsuperscript{245,249} and similarly amongst nine epilepsy patients in Brazil.\textsuperscript{250} One further US-based study on bioequivalence of anti-epileptic products showed small confidence limits and little variation in AUC and Cmax for lamotrigine.\textsuperscript{246} It does however make sense to minimise the number or frequency of changes between products whether they be originator or generic switches in order to avoid confusion. The reasons for multiple switches are beyond the scope of this study, but are likely to be in part due to the dispensing pharmacist and in part to patient preferences. Pharmacy loyalty by the nature of New Zealand's healthcare system can be expected to be high, but movement of patients from one area to another or from hospital level to community might also explain some degree of brand switching.

\textit{Study Limitations}

Sample size: The total number of participants in this study was 1659, split in a ratio of approximately 3.4 non-switchers to each switcher. Retrospective sample size calculations indicate that for a power of 80% such a population is capable of detecting a standardised difference of around 0.2,\textsuperscript{251} and for higher power would be even smaller. The difference-in-differences found for the health outcomes in the study all fell below this level, and as such might indicate a type II error for these outcomes i.e. that indeed there is an effect even though one could not be measured.

Missing data: The data collection method employed in this study relies on patient identification through a valid NHI. Prior to 2007, rates for completion of NHIs were low – estimates of the order of 72% - 88% completion have been reported on in other studies.\textsuperscript{208,209} Prescriptions for lamotrigine which did not have an associated NHI (6.1%) were removed from the dataset, leaving a dataset composed of 94% of all prescriptions dispensed for lamotrigine from 1st February 2004 to 1st February 2009.
In using national datasets to determine events, those events which are self-managed by the patient or managed at the primary care level by a general practice will not be accounted for. Any change to the frequency of visits made by a patient to their general practitioner (GP) could not be measured in this study as the data are no longer captured within a national dataset. However the finding that a low proportion of patients change back to the originator brand for any reason (30-day switchback rate of 3%) likely reflects a low requirement for interventions by the GP.

Lack of diagnosis: Due to the nature of the data it is not possible to determine with precision the primary indication for which the lamotrigine was prescribed. However, during the study years 2004 to 2007 special authority for reimbursement of the cost of lamotrigine was required and was only given for the management of epilepsy. Only after a generic version of lamotrigine was subsidised in February 2007 (i.e. after the inclusion date), did access widen to include bipolar disorder.

Only 10 patients received concomitant lithium (an indicator of bipolar disorder diagnosis) in the pre-period, and a further one patient in the post-period, all of whom were non-switchers. Of the entire study cohort, 9% of switchers and 7% of non-switchers received anti-psychotic medicines in the pre-index year, and less than 6% of all participants received medicines for the treatment of migraine (not a licenced or approved use) at any time during the entire study period. Furthermore, therapy with multiple anti-epileptic medicines for approximately 70% of all the participants was apparent; making it likely that for at least the majority of participants the primary indication for which lamotrigine was being used was epilepsy.

5.1.4. Implications for Policy, Practice and Future Research

In a clear demonstration of the impact of generic reference-pricing, the annual cost of originator lamotrigine prior to the 2007 generic-reference pricing for patients in this study was approximately NS$2.3million (based on 1300 patients taking 200mg daily at NZ$150 for a month’s supply of tablets). In 2007-2008 expenditure could have been halved, based on an estimate of 1200 patients at NZ$75 per month with 8% of patients staying on or switching back to the originator brand.

However, less than one quarter of all patients switched from the originator brand to a generic. The actual savings were therefore significantly less than could have been made if more patients were encouraged to switch. No increased use of health services was associated with switching from originator lamotrigine to a generic equivalent.

There has been little decline in the price of the generic lamotrigine products since their introduction. In 2008 both available products cost approximately NZ$60 for 56 tablets of 100mg
strength. In 2013 a third generic product has been added to the Schedule at a slightly reduced price (NZ$57). PHARMAC possibly could make further gains by using competitive tendering with the incentive of the lowest priced generic product being awarded sole-supply status (contracted for a period of time to provide the entire country’s requirements).

During the period of this study there was no incentive for any of the actors involved in the prescription of lamotrigine to use generics. Doctors, pharmacists, patients and suppliers may need to be incentivised for a change to take place. One strategy employed by insurers is to award full subsidy to the preferred product and remove the subsidy (in part or in full) from the higher-priced product. The basis for such an arrangement is that the preparations are bioequivalent and that the originator is not superior and therefore should not be subsidised. This however creates an inequitable situation whereby only those who can afford to pay for it have a choice between products. This study found patients who switched to generic lamotrigine were living in areas of higher deprivation than non-switchers, and a tendency (non-significant) towards being slightly older, of Māori ethnicity and taking multiple anti-epileptic medicines was shown. This is similar to findings from the USA whereby health insurance data showed Medicaid patients, those older than 65 years and people living in certain areas of residence had increased odds of receiving a generic anti-epileptic medicine. As the price for available generic versions of lamotrigine in New Zealand are all the same there seems to be no financial incentive for either the patient or the dispensing pharmacy to use one generic over another, and some explanation for generic-to-generic switching as evidenced in this study should be sought.

Finally, the temptation to generalise findings from older studies, limited largely to carbamazepine, to the entire anti-epileptic armoury should be avoided, as therapeutic and toxicity profiles of the 2nd and 3rd generation antiepileptic medicines are dissimilar. Studies evaluating the outcomes of switching between originator and generic versions of the newer anti-epileptic medicines and more widely of other medicines should be considered, and the availability of national health datasets makes this feasible.
5.2. Risperidone

5.2.1. Introduction

In 2010 and 2011 antipsychotic medications were the top ranked therapeutic group by expenditure in New Zealand, accounting for around 9% of total pharmaceutical expenditure in the community.42,254 By June 2012 however, expenditure for antipsychotic medicines had been halved; from an annual expenditure of approximately NZ$60 million prior to June 2012, antipsychotic medicines now cost approximately NZ$30 million annually, despite a widening of access to antipsychotic medicines and increasing prescription numbers.12

A limited number of medicines are considered non-interchangeable (examples of which are digoxin, phenytoin and warfarin) where bioequivalence has not been established and the therapeutic index is narrow. Concerns linger around the interchangeability of medicines and more recently the argument against substituting originator brands with generics has been extended to generic-to-generic switching, in particular with psychotropic medicines.28,52,255-257 Available reviews of brand-to-generic switching of psychotropic medicines have intertwined the literature on anti-epileptic medicines with those used to manage mental health conditions such as depression and psychoses, and older medicines with newer ones, blurring the picture on each of these distinct pharmacological entities.255,256

NZ policy on funding for risperidone

Risperidone is registered for use in New Zealand for the treatment of schizophrenia and other psychotic disorders, treatment and long-term control of mania in bipolar disorder, treatment of behavioural and psychological symptoms of dementia, conduct and other disruptive disorders in children, adolescents and adults and of autism in children and adolescents. In December 2008 a widening of conditions allowing non-specialist prescribing of risperidone was introduced in New Zealand. At the time, the two available brands (Risperdal and Ridal) were equally and fully subsidised.258

In March 2010 generic reference pricing was applied to all brands of risperidone tablets with the exception of the Jansen-Cilag brand Risperdal which had negotiated protection until July 2012.259 Other dosage forms such as the oral solution and injection remained subsidised at their previously agreed levels. In July 2012 the price protection afforded to the Risperdal brand expired and generic reference pricing conditions now applied to all available risperidone brands. The manufacturers did not however reduce the cost of Risperdal to the reference price level, creating a situation where patients had to either pay for the Risperdal brand or switch to a generic (see Figure 5.2). This cost difference amounted to NZ$11 to NZ$48 per month (as at
2013) depending on the strength of the tablet. The maximum amount a patient would pay for a years’ supply of subsidised risperidone is $20 (being co-payments for 4 prescriptions of 90-day supply each), whereas Risperdal for one year would cost a patient between NZ$150 to NZ$600 depending on their dose.236

Figure 5.2: Subsidy (manufacturer’s price; NZ$) for 60 x 2mg tablet of different brands of risperidone over time (source: PHARMAC Schedule)

This study thus sought to test the hypothesis that patients who switch from originator brand risperidone to generic risperidone fare no worse than those who do not make a switch, by evaluating patient health outcomes and any changes in healthcare costs consequent to the implementation of generic reference pricing of risperidone.

Study parameters

A retrospective study using the national health and pharmacy claims data sets was undertaken of all patients from 12 years of age onwards in New Zealand using risperidone tablets during the period 1st February 2010 to 31st August 2013. Prescriptions for the injectable form of risperidone as well as the oral solution and oro-dispersible forms were excluded as these forms were not affected by PHARMAC pricing policies during the same time periods. Prescriptions for risperidone during 1st February 2010 and 31st August 2013 which did not have an associated NHI (2.8%) were removed from the dataset.

The risperidone study index date was set at 1st July 2012 as this is the date on which the subsidy for the Risperdal brand was reduced and co-payment increased.
Two cohorts were constructed. A Risperdal cohort comprised all patients who had been dispensed the Risperdal brand of tablets at least 4 consecutive times within a 6 months period prior to 01 July 2012. Similarly a comparator cohort was constructed being all patients taking the Ridal brand of risperidone for at least 6 months prior to the same index date.

5.2.2. Results

Demographics of the cohorts

Demographics of both the Risperdal and Ridal cohorts are given in Table 5.2.1, and of the switcher and non-switcher groups in Table 5.2.2. All demographics for the risperidone cohorts were equal except for a higher proportion of Ridal users living in areas with an index of greater deprivation than Risperdal users.

Table 5.2.1: Demographics of the Ridal and Risperdal cohorts

<table>
<thead>
<tr>
<th>Measure</th>
<th>Ridal Cohort (n=714)</th>
<th>Risperdal Cohort (n=2372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>52.8</td>
<td>51.7</td>
</tr>
<tr>
<td>Aged &gt;65yrs (%)</td>
<td>21.4</td>
<td>20.6</td>
</tr>
<tr>
<td>Female (%)</td>
<td>47.1</td>
<td>48.7</td>
</tr>
<tr>
<td>European (%)</td>
<td>70.2</td>
<td>69.4</td>
</tr>
<tr>
<td>Māori and Pacific Peoples (%)</td>
<td>22.1</td>
<td>21.0</td>
</tr>
<tr>
<td>Mode index of deprivation (NZDep)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Proportion living in area of most deprivation (NZDep of 7-10) (%)</td>
<td>60.7 *</td>
<td>51.5 *</td>
</tr>
<tr>
<td>Proportion with no additional comorbidity (%)</td>
<td>21.3</td>
<td>18.7</td>
</tr>
<tr>
<td>Mode Comorbidity count</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Comorbidity of 3 or more (%)</td>
<td>27.6</td>
<td>30.5</td>
</tr>
<tr>
<td>Risperidone as monotherapy (%)</td>
<td>73.7</td>
<td>74.3</td>
</tr>
</tbody>
</table>

* Significantly different at 95% confidence level

In the Risperdal cohort 75% of patients switched to a fully subsidised brand, whilst the remainder continued using the Risperdal brand. Risperdal switchers were slightly younger, lived in more affluent areas, had less comorbidity, and less representation by Māori and Pacific peoples than their non-switcher counterparts (see Table 5.2.2). Although these differences were statistically significant, correlation with switching for these variables was weak.

Even in the absence of an imperative to switch, 13% of patients in the Ridal cohort made at least one brand switch and the demographics of these Ridal switchers have been presented in Table 5.2.2, alongside the demographics of the other study groups. Aside from age, no significant differences in demographic measures existed between Ridal switchers and non-switchers.

A multivariable logistic regression was conducted for switch predictors for both Risperdal and Ridal cohorts, revealing little beyond that of the binary regression analysis.
Table 5.2.2: Comparison of switcher and non-switcher group’s demographics for both Ridal and Risperdal cohorts

<table>
<thead>
<tr>
<th></th>
<th>Ridal</th>
<th></th>
<th>Risperdal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Switcher</td>
<td>Non-switcher</td>
<td>Sig. p value; (Pearson Correlation)</td>
<td>Switcher</td>
</tr>
<tr>
<td>Proportion (%)</td>
<td>13.3</td>
<td>86.7</td>
<td>-</td>
<td>75.0</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>49.6</td>
<td>53.3</td>
<td>0.027; (0.07)</td>
<td>51.3</td>
</tr>
<tr>
<td>Female (%)</td>
<td>41.1</td>
<td>48</td>
<td>0.208</td>
<td>49.6</td>
</tr>
<tr>
<td>Māori or Pacific Peoples (%)</td>
<td>29.5</td>
<td>21</td>
<td>0.063</td>
<td>19.5</td>
</tr>
<tr>
<td>NZDep 7-10 (most deprived) (%)</td>
<td>65.3</td>
<td>60.0</td>
<td>0.331</td>
<td>49.8</td>
</tr>
<tr>
<td>Comorbidity of 3 or more (%)</td>
<td>23.2</td>
<td>28.3</td>
<td>0.399</td>
<td>28.9</td>
</tr>
</tbody>
</table>

**Switch behaviour**

Time to switch: Switching can be expected to be timed around the collection of the next month’s supply of medicines (although not all patients receive a monthly supply, with some being more closely monitored and lesser amounts dispensed at a time). The mean time to switch for Risperdal was 21 days from the index date, with a range of 90 days prior to the index date (i.e. early switchers) to the cut-off date of 270 days (9 months).

Switch-back: A switch back to the previous brand within 30 days (i.e. before the next monthly dispensing is due) was made by 1.5% of Risperdal switchers. This is likely to be indicative of a patient returning to the pharmacy or prescriber to request the previous brand; however, as noted above not all patients receive monthly dispensings.

Multiple switches: Approximately 50% of Risperdal switchers made a single switch, with 40% making at least two switches during the 270 days post-index. Nearly 9% of these switchers made at least 3 switches (i.e. 4 different brands).
Health outcomes

Prescription medicines use

Unique prescription medicines for one year: The indicator of unique prescription medicines was used to measure any concomitant prescribing which might have occurred as a result of any side effects (e.g. nausea, headache) consequent to switching. No significant post-pre difference in the unique prescription count between Risperdal switchers and non-switchers was found, and a small difference was found between Risperdal switchers and the comparator Ridal non-switcher group, in favour of switchers (marginally less unique prescription medicines over a one-year period. (See Table 5.2.3)

Use of antipsychotic medicines for 6 months: For 2.7% Risperdal non-switchers and 2.6% of Risperdal switchers another antipsychotic medicine was added within 6 months of switching, whereas this was 3.1% for the Ridal non-switcher comparator group. However, differences between switchers and non-switchers and between Risperdal switchers and Ridal non-switchers were not significant.

Change in Dose: Complete dosage data was available for 84.7% of the Ridal cohort and 68.8% of Risperdal users. The majority of patients (>95%) had no dosage adjustment in the 6 months post-index which might otherwise have indicated a loss in therapeutic efficacy. No difference in the change in dose was found for Risperdal switchers versus non-switchers or versus the Ridal comparator group.

Reports to CARM

In the years from 2008 to 2013 a total of 112 reports of adverse events were received by CARM for risperidone. Of these, 9 reports related to a switch in risperidone brand, 4 indicating a reduction in therapeutic response and the remaining 5 reporting adverse reactions. The information on which product was involved in these reports is not available.

Use of health services

No difference in the use of health services, including use of the emergency department, specialist outpatient services and admissions to hospital, were found for any comparison between the Risperdal switchers and non-switchers and versus Ridal comparator group (see Table 5.2.4).

Mortality: Amongst the Risperdal group 22 switchers died within six months of their individual switch dates (0.9%) and 16 non-switchers died (0.7%). There were 10 Ridal non-switchers
deaths. The mean age of all risperidone deaths was 69 years (median 70.5 years, 25th percentile = 58 years).

*Healthcare costs:*

As no significant differences were found in healthcare utilisation between switchers and non-switchers, there would be no difference in healthcare costs. Therefore no attempt was made to estimate healthcare costs.
Table 5.2.3: Medicine use outcomes for (a) Risperdal switchers versus Risperdal non-switchers; and (b) Risperdal switchers versus comparator Ridal non-switcher group

<table>
<thead>
<tr>
<th>Change* in medicine use outcome</th>
<th>Risperdal Switcher (n = 1778)</th>
<th>Risperdal Non-switcher (n = 594)</th>
<th>Ridal Non-switcher (n = 619)</th>
<th>(a) Diff in Differences Risperdal switchers vs Risperdal non-switchers (p value; Cohen’s d value)</th>
<th>(b) Diff in differences Risperdal switcher vs Ridal non-switcher (p value; Cohen’s d value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique prescription medicine count/one year</td>
<td>-0.14</td>
<td>0.12</td>
<td>0.334</td>
<td>-0.26; (0.237; 0.05)</td>
<td>-0.47 ; (0.01; -0.15)</td>
</tr>
<tr>
<td>Use of additional antipsychotic medicines within 6 months</td>
<td>0.051</td>
<td>0.07</td>
<td>0.048</td>
<td>-0.02 ; (0.121; 0.08)</td>
<td>0.002 ; (0.54; 0.01)</td>
</tr>
<tr>
<td>Dose adjustment within 6 months</td>
<td>0.006</td>
<td>-0.01</td>
<td>-0.001</td>
<td>0.02; (0.631; -0.02)</td>
<td>0.01; (0.451; 0.03)</td>
</tr>
</tbody>
</table>

*Difference between post- and pre-period outcome

Table 5.2.4: Health service use outcomes for (a) Risperdal switchers versus Risperdal non-switchers; and (b) Risperdal switchers versus comparator Ridal non-switcher group

<table>
<thead>
<tr>
<th>Change* in use of health service</th>
<th>Risperdal Switcher (n = 1778)</th>
<th>Risperdal Non-switcher (n = 594)</th>
<th>Ridal Non-switcher (n = 619)</th>
<th>(a) Diff in Differences Risperdal switchers vs Risperdal non-switchers (p value; Cohen’s d value)</th>
<th>(b) Diff in differences Risperdal switcher vs Ridal non-switcher (p value; Cohen’s d value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Dept. (7 days post)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Emergency Dept. (30 days)</td>
<td>0.002</td>
<td>0.024</td>
<td>0.010</td>
<td>-0.02 ; (0.12; 0.06)</td>
<td>-0.01 ; (0.55; 0.05)</td>
</tr>
<tr>
<td>Outpatient (30 days)</td>
<td>0.021</td>
<td>0.003</td>
<td>0.011</td>
<td>0.02 ; (0.28; 0.04)</td>
<td>0.01 ; (0.52; 0.04)</td>
</tr>
<tr>
<td>Outpatient (180 days)</td>
<td>-0.024</td>
<td>-0.015</td>
<td>-0.048</td>
<td>-0.01 ; (0.87; 0.01)</td>
<td>0.02 ; (0.54; 0.03)</td>
</tr>
<tr>
<td>Hospitalisations (30 days)</td>
<td>0.001</td>
<td>0.01</td>
<td>-0.001</td>
<td>-0.01 ; (0.44; 0.03)</td>
<td>-</td>
</tr>
<tr>
<td>Hospitalisations (180 days)</td>
<td>-0.005</td>
<td>-0.059</td>
<td>-0.084</td>
<td>0.05 ; (0.51; 0.03)</td>
<td>0.08 ; (0.16; 0.05)</td>
</tr>
</tbody>
</table>

*Difference between post- and pre-period outcome
5.2.3. Discussion:

No difference in any outcome measure could be found for patients who switched from the originator brand of risperidone to a generic equivalent when compared with either their non-switcher counterparts or with non-switcher users of a generic risperidone. No adverse effect of the generic reference pricing policy on users of the originator brand of risperidone was found, aside from 4 case reports suggesting a loss in therapeutic efficacy. Use of healthcare services did not change for switchers, and no difference in the use of other antipsychotic medicines or dosage was found.

This study also revealed significant switching between brands; from the anticipated switch of originator to generic, as well as from generic to generic and from generic to originator and back again. Around half of the switcher cohort made a single switch but almost 10% made 3 or more switches. In a consultation document in 2010, PHARMAC noted that “up to a quarter of all patients had switched brands of risperidone [...] at least once”\textsuperscript{259}, a figure that is somewhat lower than revealed in this study.

Relevance to the literature

Literature reviews exist evaluating generic psychotropic medicines and the issue of switching,\textsuperscript{255,256} however, such reviews consider antipsychotic medicines alongside antiepileptic medicines, and typical antipsychotics against the atypical ones, medicines which have entirely different pharmacological properties and should not be clustered. Few published reports of risperidone bioequivalence studies exist,\textsuperscript{260-262} aside from those conducted for product registration. Very few case reports of adverse events related to changing between brands of risperidone exist in the literature,\textsuperscript{255,263} especially considering that there are 195 pharmaceutical companies selling generic risperidone in at least 35 countries.\textsuperscript{264} In the absence of head-to-head clinical trials between risperidone brands and limited information available in the literature, natural experiments such as this one using national datasets where both a control cohort is available as well as cases serving as their own controls, provide the best available evidence for generic equivalence.\textsuperscript{191,193}

Study Limitations

Sample size: There were 3 Risperdal switchers (n=1778) for every Risperdal non-switcher (n = 594) and similarly for the comparator Ridal non-switchers (n = 619). Retrospective sample size calculations indicate that for a power of 80% a population of approximately 3000 risperidone patients is capable of detecting a standardised difference of around 0.05,\textsuperscript{251} and for
higher power would be even smaller. The difference-in-differences found for the health outcomes in the study all fell below this level, and as such might indicate a type II error for these outcomes i.e. that indeed there is an effect even though one could not be measured. As a measure of effect size, values for Cohen’s d test were calculated and are included in the outcomes tables.

Use of ancillary health services: Mental health services are delivered in New Zealand by a network of the community mental health team, case managers and other support workers, all of whom are in frequent contact with the patient and are better placed to notice signs of relapse or loss in therapeutic efficacy. Such contacts are however not noted in the national health datasets. In addition, any change in the frequency of visits made by a patient to their general practitioner (GP) could not be measured in this study as these data were also not captured within the national datasets during the period of this study. An attempt to address this limitation has been made by evaluating changes in medication (dosage and add-on therapy); however, any change in the frequency of patient contacts not resulting in a change in therapy will not be accounted for by this outcome measure.

Diagnosis: Likewise, due to the nature of the data, it is not possible to determine with precision the primary indication for which the risperidone was prescribed. Aside from schizophrenia, risperidone is also used for the treatment of behavioural and psychological symptoms of dementia, and other conditions such as mood and anxiety disorders. 18% of all risperidone patients were older than 65 years, and 7% were aged 75 years or older; such patients possibly being candidates for receiving risperidone for dementia.

5.2.4. Implications for Policy, Practice and Future Research

Although the prevalence of schizophrenia is low (up to 1% of the population\textsuperscript{204,265,266}) total healthcare costs for this illness can be considerable. Data from the US gives total annual costs ranging from US$33-63 billion with hospitalisation being the biggest contributor to the cost of illness for schizophrenia.\textsuperscript{204,265} The cost of medication generally accounts for less than 10% of the total cost in schizophrenia; however with the use of newer antipsychotics in the pipeline the cost of medicines proportionally might well increase.\textsuperscript{267} (Consequent expenditure on hospitalisation could also decrease if these newer medicines offer greater efficacy). At the national level in New Zealand, all forms of risperidone, including injectable, accounted for approximately 2% of the total annual community pharmaceutical budget in 2010 and 2011 (NZ$14 million per year). Following generic reference pricing of the tablet only a small decrease in risperidone expenditure has been achieved (NZ$13 million in 2013)\textsuperscript{12} with the cost of the injection remaining unchanged since 2008 and accounting for the majority of the expenditure.\textsuperscript{259}
Aside from the concern with respect to multiple switching facilitated by the existence of three generic brands, the price of the generics is higher in New Zealand (~US$10 for 60 x 2mg tablets) than the International Median Price (US$2.7 \textsuperscript{268}) and the British National Formulary price (GBP1.5 \textsuperscript{269} or US$2.5). The introduction of price competition between these generics and awarding exclusivity for the market to one supplier could potentially achieve further savings as well as minimise the extent of between-brand switching.
5.3. Olanzapine

5.3.1. Introduction

Olanzapine, an atypical antipsychotic medicine used in the management of schizophrenia and related psychoses, has been widely available internationally since 1996, and in New Zealand (NZ) since 1999. Until patent expiry in 2011, olanzapine was a relatively expensive medicine and in NZ singly accounted for more expenditure (~NZ$30million) than any other medicine in 2010.

NZ Policy on funding for olanzapine

In June 2011 generic reference pricing was applied to olanzapine, and two more brands of olanzapine were listed in the NZ Pharmaceutical Schedule for subsidy. The manufacturer of the originator Zyprexa brand did not reduce their price to meet the reference price and currently (2014) 28 x 10mg tablets of Zyprexa is priced at NZ$200 (US$173) whilst the cost of generic olanzapine in NZ is less than 4% of the originator at NZ$6 (~ US$5.2).

Large differences in the price of generic versus originator olanzapine similarly exist in most countries. For example the British National Formulary reports that 28 tablets of 10mg generic olanzapine costs £1.51 compared with £87.40 for the same amount of the originator brand. Generic olanzapine (at 6% of the cost of originator) has been produced in Canada since 2009, but has been the focus of litigation with the originator company until 2012.

5.3.2. Study parameters

A retrospective study was undertaken of all adult patients (aged 14 years or older) in NZ who had been dispensed olanzapine tablets at least 5 times during the 6 months prior to the introduction of generic olanzapine (01 June 2011) and also for the 6 month period prior to 01 June 2010 (i.e. one year earlier). From this group, patients who switched to generic olanzapine from Zyprexa following the withdrawal of subsidy payments for Zyprexa on September 1st 2011 (i.e. the ‘intervention’) were identified. Individual ‘switch dates’ (the date of the intervention) were noted and the time taken to switch was calculated from 01 September 2011, this being the date of change in subsidy for the originator brand.

Likewise ‘non-switchers’ were also identified with the intention of comparing switchers with non-switchers; however, only 16 patients did not switch to generic olanzapine and were excluded from the study, being too small a cohort to use as a control group. Instead, outcomes were evaluated for the switchers, during an earlier no-intervention period. An ‘index date’ was computed for each patient, being one year earlier than their switch date, in order that
comparison could be made between intervention and no-intervention periods, with patients acting as their own controls.

**Figure 5.3 Schematic representation of determination of outcome measures**

![Schematic diagram](image)

Note: Generic reference pricing was instituted on 1st June 2011. Switch dates were determined for each of the 5223 included patients, and an 'index date' was assigned to each patient, being one year earlier. The number of events for each outcome measure was determined pre- and post-index date and pre- and post-switch date, allowing the outcome 'difference in differences' to be calculated.

### 5.3.3. Results

**Demographics of the cohorts**

A description of the study population is given in Table 5.3.1. The majority of all patients (98%) had switched within 3 months of implementation of the pricing policy, with a large proportion having switched ahead of the policy date on 1st Sept 2011. The mean time to switch was thus negative 22 days (standard deviation = 53.5 days).

**Switch behaviour**

In the one-year follow up, 12.5% of study patients made a single switch whilst 86% switched from the originator brand to a generic and then a further switch on to a second generic brand. A small percentage of patients (1.4%) switched from originator to generic, back to originator and then to generic again.
Table 5.3.1: Baseline demographics of olanzapine cohort

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Finding (n=5223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (adults only) (years)</td>
<td>53.2</td>
</tr>
<tr>
<td>Aged &gt;65 years (%)</td>
<td>22.7</td>
</tr>
<tr>
<td>Aged &gt;80 years (%)</td>
<td>7.1</td>
</tr>
<tr>
<td>Female (%)</td>
<td>46.3</td>
</tr>
<tr>
<td>European (%)</td>
<td>70.4</td>
</tr>
<tr>
<td>Māori and Pacific Peoples (%)</td>
<td>22.1</td>
</tr>
<tr>
<td>Proportion living in area of most deprivation (NZDep of 7-10) (%)</td>
<td>56.5</td>
</tr>
<tr>
<td>Proportion with no additional comorbidity (%)</td>
<td>21.4</td>
</tr>
<tr>
<td>Comorbidity of 3 or more (%)</td>
<td>35.8</td>
</tr>
<tr>
<td>Study medicine as monotherapy (%)</td>
<td>71.2</td>
</tr>
</tbody>
</table>

Health outcomes

Medicine indicators

*Change in Use of antipsychotic medicines:* For 71% of patients the only antipsychotic medicine received was olanzapine. The small increase in 6 month use of additional oral antipsychotics post-switching (0.02) was less than the increase observed during the same 6-month period one year earlier (0.12), with the mean use of additional oral antipsychotic medicines per person decreasing over the entire study time period (-0.1/person; p=0.00).

Most of the study patients (94.8%) did not receive any injectable antipsychotic medicines throughout the study period. No significant change in use of injectable antipsychotic medicines 6 months after switching was found for the 273 patients who had received injections in the 6 months prior to the switch. Comparing the post-pre difference around the switch date with the same 6 month period from one year earlier, fewer injections were used in these same patients post-switching; (difference-in-differences = -0.92; p= 0.00). See Table 5.3.2.

*Change in Dose:* Complete dosage information was available for 2211 patients over the study period (42% of the study group). A mean dose of 12.28mg (S.D. of 9.1mg) was found for these patients pre-switching. For the majority (95%) no change in total daily dose was observed 6 months post-switching (mean dose post-switch = 12.20mg; SD 9.1mg). However, dosage information was incomplete for the remaining 58% of the study cohort.

*Cessation of olanzapine therapy:* Fifty-two patients (1%) did not receive any further dispensings of olanzapine after switching and a further 31 patients only received one further prescription after switching. The proportion of patients discontinuing olanzapine within 8 weeks of switching was therefore 1.6% in total.
Change in number of unique prescription medicines: A significant but small decrease in the number of unique prescription medicines was found during the intervention (post-switch) year compared with the no-intervention year (-0.41; p= 0.00).

Table 5.3.2: Summary of Medicine Indicators

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to switch (days)</td>
<td>-22 days (range -92 to &gt;365 days)</td>
</tr>
<tr>
<td>% making a single switch</td>
<td>12.5%</td>
</tr>
<tr>
<td>% with no dose change (180 days); n= 2211</td>
<td>95%</td>
</tr>
<tr>
<td>% stopping olanzapine therapy (180 days)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Change in oral antipsychotic add-on therapy (180 days)</td>
<td>-0.10*; p=0.00</td>
</tr>
<tr>
<td>Change in use of antipsychotic injection (180 days); n= 273</td>
<td>-0.92*; p=0.00</td>
</tr>
<tr>
<td>Change in unique prescription medicines count (365 days)</td>
<td>-0.41*; p=0.00</td>
</tr>
</tbody>
</table>

* i.e. less in the year following switching than the year before

Adverse reaction reporting:

Between 2008 and 2013, 110 reports relating to olanzapine were received by the national pharmacovigilance centre CARM. During the study years 2011-12 CARM received 38 reports related to olanzapine, 12 of which involved switching brands. A reduced therapeutic response was suspected in 4 cases, with the balance unspecified adverse reactions.238

Health service use

No significant difference in the use of any of the measured health services (emergency department, specialist outpatient services and admissions to hospital) was found at either 30 days or 180 days post-switching when compared with the same time period one year earlier (see Table 5.3.3). No correlation was found between patients making multiple switches and utilisation of health services.

Mortality

There were 41 deaths amongst the 5223 study patients (rate of 0.008) in the 3 months following brand switching, with the mean age of these patients being 71.5 years (median = 77.3 years). No deaths recorded medication issues as the primary or secondary cause of death; with 11 deaths subject to coroner’s findings at the time of the study. Of the entire study cohort, 144 patients had died within 1 year of switching (rate of 0.028), in line with the death rate found for people with a diagnosis of a psychotic disorder in NZ (being 3 times the national death rate of 0.008 for adults in 2011).8,273
Table 5.3.3: Summary of Healthcare Indicators (n=5223)

<table>
<thead>
<tr>
<th>Health Service used</th>
<th>Change* on switching to a generic brand; intervention</th>
<th>Change* one-year earlier, no-intervention</th>
<th>Difference-in-Differences (95% CI); significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Dept. at 30 days</td>
<td>0.024</td>
<td>-0.003</td>
<td>0.027 (-0.01 to 0.06); 0.16</td>
</tr>
<tr>
<td>Specialist outpatient at 30 days</td>
<td>-0.011</td>
<td>-0.015</td>
<td>0.004 (-0.03 to 0.04); 0.82</td>
</tr>
<tr>
<td>Specialist outpatient at 180 days</td>
<td>-0.056</td>
<td>0.023</td>
<td>-0.079 (-0.25 to 0.09); 0.35</td>
</tr>
<tr>
<td>Hospitalisations at 30 days</td>
<td>0.005</td>
<td>-0.002</td>
<td>0.007 (-0.003 to 0.02); 0.18</td>
</tr>
<tr>
<td>Hospitalisations at 180 days</td>
<td>0.013</td>
<td>-0.013</td>
<td>0.026 (-0.001 to 0.05); 0.06</td>
</tr>
</tbody>
</table>

* Difference in use of health service between post- and pre-intervention (switch) period

5.3.4. Discussion:

Impact of switching

This study found no increase in hospitalisations, use of emergency or specialist outpatient services, or untoward health events in patients following switching from Zyprexa to generic olanzapine. No changes in dosage and no increase in the mean use of additional oral or injectable antipsychotic medicines per person were found. The rate of spontaneous adverse event reporting was similar to the rate of reports to CARM for risperidone during the same 2008-2013 period. The rate of death following switching was not significantly different from death rates reported for New Zealanders with a diagnosis of a psychotic disorder, or from adult users of risperidone in NZ.

Reviews which evaluate generic psychotropic medicines and the issue of switching are available in the literature; however, reports which extrapolate the effects of typical antipsychotics against the pharmacologically different atypical ones should be met with caution. Little evidence is available for the relatively newer atypical antipsychotic medicines such as olanzapine, and few published reports of olanzapine bioequivalence studies exist aside from those conducted for product registration. Very few case reports of adverse events related to changing between brands of olanzapine exist in the literature, despite around 100 pharmaceutical companies selling generic olanzapine throughout the world. With limited information available in the literature and a lack of head-to-head clinical trials between different olanzapine brands, observational studies such as this one using national datasets provide the best available evidence for equivalence of generic and originator brand medicines.
Switching behaviour

Notably, the majority of patients (86%) made multiple switches between available generic brands. This may be incidental switching within or between community pharmacies, or it might be a consequence of different generic brands being used between levels of care. For example, currently (in 2014) there are 2 generic brands of olanzapine on the Hospital Medicines List and 3 brands available within the community sector. PHARMAC initially only managed the Community Pharmaceutical Schedule, but in 2010 was tasked with managing hospital medicines, which should see a closer alignment of medicine lists between hospital and community-based care and reduce the impact of patient movement through the health sector on switching between different generic brands. The impact of making multiple switches is unclear. Beliefs about medication are regarded as an important predictor of non-adherence to treatment, which in turn is associated with readmissions and increased healthcare costs.\(^206,280,281\) There is little literature quantifying the specific impact of switching on adherence, and none on the impact of multiple switches; however, changes in appearance of a particular medicine may be viewed with suspicion and in turn may impact on non-adherence.\(^207\) Although multiple switching within short periods of time is probably undesirable, this study found no correlation between multiple switches and healthcare outcomes.

5.3.5. Policy implications

Of the more than 5000 patients consistently using olanzapine medication in NZ during the time of this study, only 16 patients did not switch to generic olanzapine following the withdrawal of subsidy payments for the originator brand of olanzapine tablets on September 1st 2011. A rapid and almost complete switch to generic olanzapine with no adverse health outcomes reflects the desired outcome of NZ’s policy of generic reference-pricing in savings made to the annual community pharmaceutical budget.

At the average dose of olanzapine received by patients in this study of 12.5 mg (nearest tablet size to 12.28mg), a year’s supply of originator olanzapine would cost NZ$ 3,322.28 today whilst that of the generic costs NZ$ 108.55. The savings over a year for the patients in this study alone amounts to NZ$16 million (NZ$ 16,611,400.00 for originator versus for NZ$ 542,750.00 generic olanzapine).\(^282\)

Study Limitations

Ideally, the availability of a comparator group of olanzapine non-switchers would have made the findings more robust. However, this evaluation includes the post-pre differences in
measures one year earlier for each patient, using the switcher patients as their own non-
switcher controls, and in doing so also eliminates between group confounders.

In using national datasets to determine events, those events which are self-managed by
the patient will not be accounted for. Additionally, any change in the use of the general
practitioner, or of the network of the community mental health team, case managers and other
support workers could not be measured in this study as the data were not captured within a
national dataset during this time.

Ad hoc or rescue use of injectable antipsychotic medicines within the GP practice is most
often not recorded in the PHARMS database on a named patient basis, and thus will be missing
from the data. It is also noted that although the dispensing of a medicine does not equate to
actual use, information collected in pharmacy databases are generally recognised as a
reasonable approximation of medicine use.191
5.4. Venlafaxine

5.4.1. Introduction

Depression affects more than 130 million people worldwide, with an estimated lifetime prevalence of 10-15%. It carries a burden of illness in itself and has been associated with greater rates of mortality following myocardial infarction and stroke, and 20-fold increases in the rate of death from suicide. In addition, decreased workplace productivity and psychosocial disability are key features of depression. The World Health Organization suggests that by 2030 depression will be the leading cause of disease burden, with the disease affecting both developed and developing countries.

The lifetime risk for a major depressive illness in New Zealand has been estimated to be approximately 25% with a median age of onset occurring in the early 30s. It is expected that one in four adults will experience an episode of major depression in their lifetime. Alongside psychosocial therapy, antidepressant medicines form the mainstay of treatment with selective serotonin reuptake inhibitors (SSRI) usually being the first choice of antidepressants. The advent of venlafaxine - a serotonin-noradrenaline reuptake inhibitor (SNRI) - in the late 1990s offered an additional treatment option in the antidepressant armoury alongside related SSRIs, despite higher rates of adverse events.

5.4.2. NZ policy on funding for venlafaxine

In New Zealand (NZ) the use of venlafaxine has generally been reserved for ‘treatment-resistant’ depression where a trial of at least two other antidepressant medicines has not been successful. The originator brand Efexor-XR was introduced on to the NZ market and subsidized by the government in early 2004, with special restrictions requiring prescriptions to be initiated only by a psychiatrist to limit usage whilst increasing experience with the medicine. In 2007 access was widened to include psychiatric registrars and vocationally registered general practitioners and usage of the medicine increased. In mid-2011 a less expensive generic version of venlafaxine (Arrow-Venlafaxine XR) became available, subject to the same prescribing and subsidy conditions as the originator brand.
5.4.3. Study parameters

A retrospective study using the national health and pharmacy claims data sets was undertaken of all adult patients in New Zealand using venlafaxine during the period from 01 February 2011 to 01 August 2013.

Study cohorts were constructed using the pharmacy dataset to identify both new users of venlafaxine (either brand) and patients using it continuously for at least 6 months prior to the introduction of the generic on 1st August 2011, (see Figure 5.4.1: Construction of venlafaxine study cohorts). Adults patients who received a continuous supply of originator venlafaxine (prescriptions dispensed covering at least 168 days) in the 6 months preceding 01 Aug 2011 formed the ‘existing user’ cohort (n =10,212). Two further cohorts were constructed being patients using venlafaxine for the first time between 01 August 2011 and 31 July 2012 and for 6 successive months; one of new users of the originator venlafaxine (n=3,819) and another for the generic venlafaxine (n=201).

A start date of 01 August 2011 was assigned to the existing users, whilst individual start dates were noted for new users of venlafaxine, and the time taken to switch calculated (days). For the non-switcher patients an index date was randomly assigned to each using the dates from the switchers to achieve a matching proportion of index dates amongst the non-switchers upon which ‘before’ and ‘after’ outcomes could be measured. Follow-up was conducted for a period of 12 months post-switch (for switchers) or post-index (for non-switchers).
5.4.4. Results

Demographics of the cohorts

In the first six months following the introduction of generic venlafaxine in the PHARMAC Schedule, uptake of the generic brand was low with only 201 new generic users (5%) meeting the inclusion criteria compared with 3,819 new users of originator venlafaxine (Note that this does not necessarily reflect all users of venlafaxine in New Zealand, rather only those for whom a continuous 6 month supply could be identified from the PHARMS database). Table 5.4.1 shows the characteristics of the cohorts, and Table 5.4.2 of the switchers and non-switchers.
Table 5.4.1: Key demographic characteristics of the three venlafaxine cohorts

<table>
<thead>
<tr>
<th></th>
<th>Existing originator users</th>
<th>New originator users</th>
<th>New generic users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10,212</td>
<td>3,819</td>
<td>201</td>
</tr>
<tr>
<td>Male</td>
<td>35%</td>
<td>36%</td>
<td>41%</td>
</tr>
<tr>
<td>European</td>
<td>88%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>Māori &amp; Pacifica</td>
<td>6%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Living in area of high socio-economic deprivation</td>
<td>41%</td>
<td>41%</td>
<td>43%</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>49</td>
<td>45</td>
<td>44</td>
</tr>
</tbody>
</table>

*Existing originator users had been using originator brand venlafaxine for at least 6 months before the policy date (1st August 2011), whilst new users had not been exposed to venlafaxine (either brand) before that date.

Non-switchers were slightly older than switchers in both new user cohorts, whilst a higher proportion of switchers lived in areas of greater deprivation (NZDep 7-10). For new users of generic venlafaxine the apparent difference in deprivation index did not reach statistical significance, possibly because of the small size of the group. Venlafaxine was used as monotherapy slightly less in existing non-switcher users than switchers, but equally in the new user cohorts.

Table 5.4.2: Key demographic characteristics of switchers versus non-switchers by cohort

<table>
<thead>
<tr>
<th></th>
<th>Existing originator users</th>
<th>New originator users</th>
<th>New generic users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Switcher (n=9036)</td>
<td>Switcher (n=1176)</td>
<td>Non-Switcher (n=3371)</td>
</tr>
<tr>
<td>Proportion (%)</td>
<td>88.5</td>
<td>11.5</td>
<td>88.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>34.6</td>
<td>37.3</td>
<td>36.3</td>
</tr>
<tr>
<td>European (%)</td>
<td>87.7</td>
<td>87.7</td>
<td>85.9</td>
</tr>
<tr>
<td>Māori &amp; Pacifica peoples (%)</td>
<td>6.0</td>
<td>6.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Living in area of high socio-economic deprivation (%)</td>
<td>40.4</td>
<td>42.3</td>
<td>39.7* (p=0.007; r=0.04)</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>48.9</td>
<td>48.4</td>
<td>45.2* (p=0.001; r=-0.05)</td>
</tr>
<tr>
<td>Median comorbidity count</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Venlafaxine as monotherapy (%)</td>
<td>67.5* (p=0.001; r=0.03)</td>
<td>72.5</td>
<td>74.9</td>
</tr>
</tbody>
</table>

*Existing originator users had been using originator brand venlafaxine for at least 6 months before the policy date (1st August 2011), whilst new users had not been exposed to venlafaxine (either brand) before that date.

*Significant versus switcher; A switcher is a patient changing from one brand to a second brand (either originator-to-generic or generic-to-originator). Non-switchers did not make a change in brand.

The correlation of demographic factors with switch status was examined; however individual correlations were weak, with the variables only minimally accounting for the likelihood to switch. Regression analysis revealed a Nagelkerke R square value of 0.008 for the predictors of demographics and monotherapy and comorbidity (i.e. the predictors accounted for
less than 1% of variance.) Monotherapy was the only predictor indicating likelihood to switch (OR 0.80 for not switching [95% CI 0.69 - 0.92]).

**Switching patterns**

Switching between available brands was noted for a period of up to one year from August 1· 2011. Of the 10,212 existing originator brand users, the majority of patients continued using the originator brand (‘non-switchers’), with only 12% switching to the generic (see Table 5.4.3). Similarly the majority (88%) of new originator brand users did not switch. Conversely, a large proportion (almost 60%) of the generic new users made at least one brand switch.

**Table 5.4.3: Switching patterns of the three venlafaxine cohorts**

<table>
<thead>
<tr>
<th></th>
<th>Existing originator users</th>
<th>New originator users</th>
<th>New generic users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of switchers (proportion)</td>
<td>1172 (11.5%)</td>
<td>448 (11.7%)</td>
<td>118 (58.7%)</td>
</tr>
<tr>
<td>Mean days to first switch (standard deviation)</td>
<td>189 (129)</td>
<td>175 (110)</td>
<td>121 (98)</td>
</tr>
<tr>
<td>Number (%) making a single switch</td>
<td>712 (60%)</td>
<td>230 (51%)</td>
<td>84 (71%)</td>
</tr>
<tr>
<td>Proportion switching back within 14 days</td>
<td>45 (3.8%)</td>
<td>1 (0.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Number (%) making a second switch*</td>
<td>290 (24%)</td>
<td>163 (36%)</td>
<td>16 (14%)</td>
</tr>
<tr>
<td>Number (%) making 3 or more switches*</td>
<td>129 (11%)</td>
<td>54 (12%)</td>
<td>18 (15%)</td>
</tr>
</tbody>
</table>

*Existing originator users had been using originator brand venlafaxine for at least 6 months before the policy date (1st August 2011), whilst new users had not been exposed to venlafaxine (either brand) before that date.
* at any time up to one year after the first switch

Prescriptions for venlafaxine are generally written for a 3-month period, usually in one-monthly lots. The time to make the first switch was similar for both originator brand user cohorts, with a switch first occurring around 6 months from August 1· 2011. New generic users switched slightly earlier on average at 4 months from commencement.

In both originator brand switcher groups more than half made a single switch, i.e. they switched to generic venlafaxine and continued using it throughout the following year (see Table 5.4.3). Forty-five of the switchers (3.8%) from the existing user group, however, made a switch back to originator venlafaxine within 14 days of their first switch.

Twenty-four percent of existing switchers and 36% of new originator brand switchers returned to using the previously used brand (generic-to-originator). Amongst the new generic user switchers, the majority (71%) switched from generic to originator brand. Amongst all switchers more than 1 in 10 patients made multiple (3 or more) switches.

**Pharmacy and prescriber loyalty**

Most patients included in this study used a single prescriber (range 93% to 97%). Amongst all switchers combined (n=1742) 79% used a single pharmacy, compared with 94% of non-
switchers. A statistically significant but weak correlation exists between switching and number of pharmacies used \((p=0.000, \text{Pearson’s } r = 0.14)\). The maximum number of pharmacies used by a single patient was 13.

In addition, 30% of all pharmacies never dispensed generic venlafaxine between the August 1, 2011, when it became available, and January 31, 2014.

**Health outcomes**

The findings observed for existing originator brand users are summarized in Table 5.4.4, and for new users in Table 5.4.5. There were too few new users of generic venlafaxine to detect differences between switchers and non-switchers and hence the findings are not presented.

**Health services use**

For existing originator users there were no significant differences between switchers and non-switchers in all outcome measures except the lower use of specialist outpatient services over one year made by switchers; \((0.6 \text{ less visits/person})\). No differences in health services use between switcher and non-switcher new originator users were found. For all contacts made with the health system combined (composite outcome of emergency department use, hospitalizations and outpatient specialist services) no difference could be found between switchers and non-switchers at 6 months, for either new or existing users of the originator brand.

**Reports to CARM**

New Zealand’s national Centre for Adverse Reactions Monitoring (CARM) receives reports from doctors, pharmacists, patients and the pharmaceutical industry. Prior to the introduction of generic venlafaxine an average of 35 reports was received by CARM annually for originator venlafaxine. During the year 2011 immediately following the introduction of generic venlafaxine no reports of adverse events were received related to a change in brand, whilst there were 33 other adverse events reported related to venlafaxine in general. In 2012, of the 29 reports received, four related to a brand switch, and in 2013, two out of 16 reports were brand-switch related.

**Deaths**

The rate of death amongst existing originator users was the same for non-switchers (0.02) and switchers (0.02) when followed up for at least a one year after the index date. For new users of originator venlafaxine the rates were 0.01 and 0.004 for non-switchers and switchers respectively and for new generic brand users was 0.01 for both non-switchers and switchers.
Table 5.4.4: Health outcomes for switchers versus non-switchers; existing users of originator venlafaxine

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Post-pre difference: Non-switchers* (n=9036)</th>
<th>Post-pre difference: Switchers* (n=1176)</th>
<th>Difference-in-differences; (95% CI)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in visits to the ED per person (30 days)</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01 (-0.01 to 0.03)</td>
<td>0.24</td>
</tr>
<tr>
<td>Change in visits to the ED per person (6 months)</td>
<td>0.00</td>
<td>0.04</td>
<td>0.04 (-0.02 to 0.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Change in hospital admissions per person (30 days)</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01 (-0.01 to 0.03)</td>
<td>0.31</td>
</tr>
<tr>
<td>Change in annual number of hospital admissions per person</td>
<td>0.00</td>
<td>0.02</td>
<td>0.02 (-0.05 to 0.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>Change in use of specialist outpatient services per person (30 days)</td>
<td>-0.01</td>
<td>-0.03</td>
<td>-0.02 (-0.07 to 0.03)</td>
<td>0.47</td>
</tr>
<tr>
<td>Change in annual use of specialist outpatient services (visits per person)</td>
<td>-0.17</td>
<td>-0.77</td>
<td>-0.6 (-1.2 to -0.05)</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in composite outcome (6 months)†</td>
<td>-0.06</td>
<td>-0.33</td>
<td>-0.28 (-0.6 to 0.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Change in number of unique prescription medicines per person per year</td>
<td>0.00</td>
<td>0.04</td>
<td>-0.04 (-0.4 to 0.4)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*A switcher is a patient changing from originator to generic venlafaxine. Non-switchers did not make a change in brand.

† Composite outcome = all contacts made with the health system combined (emergency department use, hospitalisations and outpatient specialist services).

‡ Analysis using propensity score matching amongst the existing user group was also conducted (n= 1176 matched pairs), producing the same overall findings.

Table 5.4.5: Health outcomes for switchers versus non-switchers; new users of originator venlafaxine

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Post-pre difference: Non-switchers* (n=3371)</th>
<th>Post-pre difference: Switchers* (n=448)</th>
<th>Difference-in-differences; (95% CI)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in visits to the ED per person (30 days)</td>
<td>0</td>
<td>-0.02</td>
<td>-0.01 (-0.05 to 0.02)</td>
<td>0.56</td>
</tr>
<tr>
<td>Change in visits to the ED per person (6 months)</td>
<td>0.03</td>
<td>0.1</td>
<td>0.08 (-0.002 to 0.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Change in hospital admissions per person (6 months)</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01 (-0.06 to 0.09)</td>
<td>0.75</td>
</tr>
<tr>
<td>Change in use of specialist outpatient services per person (6 months)</td>
<td>0.07</td>
<td>0.2</td>
<td>-0.13 (-0.48 to 0.22)</td>
<td>0.47</td>
</tr>
<tr>
<td>Change in composite outcome (6 months)‡</td>
<td>0.23</td>
<td>0.19</td>
<td>-0.04 (-0.4 to 0.4)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*A switcher is a patient changing from originator to generic venlafaxine. Non-switchers did not make a change in brand.

† Composite outcome = all contacts made with the health system combined (emergency department use, hospitalisations and outpatient specialist services.)
5.4.5. Discussion

Uptake of generic venlafaxine amongst new users in New Zealand is low at 5%, and minimal switching to the generic occurs. Approximately 12% of the 14,031 originator brand users in this study switched to generic venlafaxine, whilst approximately 60% of the 201 generic users switched to the originator brand (i.e. ‘reverse-switching’). No net effect on health service use, however, could be found for either new or existing originator-to-generic brand switcher patients compared with non-switchers.

Some 4% of patients switched back to the originator brand within 2 weeks of switching, suggesting a possible adverse response to the generic brand. Despite being unable to provide a precise reason for a switch-back, such a rate is of the order expected with any medicine irrespective of brand.

The findings of this study are consistent with similar studies from NZ evaluating the effects of lamotrigine and risperidone brand switching where, despite patterns of multiple switches amongst patients, no adverse effects were evident.274,288 Further reports related to venlafaxine include a report of therapeutic drug monitoring of venlafaxine in Germany amongst 35 patients which found no difference in serum concentrations between originator brand or generic formulations,289 and another bioavailability study amongst volunteers where no difference between originator and generic formulations was found.290 Another study determined that the maximum plasma concentration between different venlafaxine preparations was initially (up to 6 hours) not the same; yet at steady state no differences could be found.291 A study from the US found that rates of discontinuation were similar for brand and generic brand antidepressants including venlafaxine, but that short-term healthcare costs and pharmacy costs were lower in new generic users.292

While consistent with the findings of the limited available research on venlafaxine, the present study extends the existing literature in several important ways. The number of patients included in this study- some 1,600 switcher and 14,000 non-switcher patients - greatly exceeds that in bioavailability studies, which often also only use healthy volunteers, adding certainty to the findings. Also, in the context of New Zealand, this study capitalizes on national policies which, when enacted, affect the total population. When a change is made in the NZ Pharmaceutical Schedule, such as that of venlafaxine, conditions of a natural experiment exist whereby the total affected population (users of venlafaxine) is exposed to the same intervention (availability of generic venlafaxine) outside of the researcher’s control: a controlled clinical trial would struggle to achieve similar parameters.
Despite these strengths, there are a number of important limitations that need to be considered when interpreting the findings of the present study. As an observational study using healthcare databases randomization is not possible, making the evaluation of potential confounders all the more important. The intergroup variability between switchers and non-switchers found in this study was limited to a single variable each (out of 7 measures) amongst existing originator and new generic users and two variables amongst new originator users. Correlation of these variables with the likelihood to switch was so low as to be negligible (see Table 5.4.2). Misclassification or incompleteness of data cannot be ruled out in these databases; however, the PHARMS database is an administrative database used for reimbursements to the pharmacy and, together with the special authority requirements, improves the reliability of the data. This study has been able to focus only on originator-to-generic brand switching and not generic-to-originator due to the low uptake of generic venlafaxine in new users. Retrospective sample size calculations indicate that for a power of 80% a population size of around 400 would be required to detect outcomes adequately amongst new generic venlafaxine users.

A follow-up period of 12-months was chosen in the case of existing users, being a period long enough to detect any health outcomes consequent to switching, and to accommodate any seasonality variation. In the case of new users, the difference-in-differences comparison could only be made for up to 6 months as the inclusion criteria required patients not are taking venlafaxine at any time in the preceding 12 months and for at least 6 months (only) from the policy index date.

Due in part to changes in the method of funding at primary care level, data on individual patient-general practitioner visits were not captured at a central level during the study years. This means that data are not available to indicate contacts made with either the dispensing pharmacy or the general practice in relation to brand switches. It is possible that a patient would seek reassurance from both the pharmacist and primary care physician if they considered a change in venlafaxine brand was problematic. This study uses two variables - the switch-back rate and the number of unique prescription medicines/year - as an indirect measure of this effect based on the knowledge that up to 70% of all visits to the doctor in NZ result in a prescription being written. Despite the fact that a dispensed medicine does not necessarily mean that the medicine has been taken, either as intended or at all, pharmacy databases are accepted as a close approximation of medicine use.

5.4.6. Implications

Switching to generic venlafaxine in this study occurred without any detectable increase in health services use, and so apparently did not impose any additional health costs. Considerable
savings could have been made had the price of generic venlafaxine been negotiated to 50% of the originator on introduction and incentives to switch created. Approximately NZ$2 million (75mg monthly dosage) in the first year might have been saved with complete switching to generic venlafaxine at 2012 prices (see Fig. 5.4.2). It is thus worth exploring the barriers to switching, or lack of incentives to switch, within the context of this study.

Figure 5.4.2: Price of venlafaxine in NZ over time

At the introduction of generic venlafaxine no incentive existed to promote its use. Despite this, 1 in 10 patients switched from originator to generic venlafaxine. Prior to September 2013 there was no incentive for either the doctor or patient to choose which brand of venlafaxine to use, as both brands were subject to the same Special Authority (SA) approval process. Since late 2013, however, generic venlafaxine no longer requires a SA for prescribing and subsidy, and this should act as an incentive for doctors to prescribe generic venlafaxine. Existing patients can continue to receive the originator brand fully funded if their doctor renews the special authority (given for 2 year periods), and, as direct-to-consumer advertising is permitted in New Zealand, the supplier of the originator brand encourages patients to insist on this.\(^{294}\) A similar situation existed in Sweden whereby the absence of demand-side activities to encourage use of generic venlafaxine led to no change in utilization. An increase in the use of venlafaxine, however, was observed when prescribing of duloxetine was restricted, and near complete generic prescribing of venlafaxine was achieved in 2011 once subsidy of the originator brand was removed in 2009.\(^{295}\) This removal of the subsidy in Sweden tested “brand worship”,\(^{296}\) whereas New Zealand has continued to fully subsidize the originator brand leaving patients (in theory) with the choice of brand. Belgium too instituted preferential reimbursement for generic SSRIs, yet found that marketing strategies - including the introduction of pseudo-generics and prescribing and consumer brand loyalty - threatened the economic gains made by the policy.\(^{15}\)
Pharmacies in NZ are contracted by the District Health Boards to provide services to patients, including dispensing medicines for which pharmacies are reimbursed. At the time of this study reimbursements for medicines dispensed were subject to a complex formula, but which in essence were calculated as a proportion (4%) of the price as gazetted in the PHARMAC Schedule.297 Thus, a disincentive to switch patients to the less expensive generic venlafaxine now exists for pharmacy owners. This is reflected in the findings that 30% of pharmacies in this study did not dispense generic venlafaxine at all, a stance PHARMAC have cautioned pharmacy owners against.282 Whether it is the pharmacy or the patient making a choice to switch or not is unclear; however, it is clear that 60% of generic users switched (or were switched) to the originator brand. Pharmacists are within the bounds of NZ law if they switch brands provided that they inform the patient of the change; the patient’s consent, although implied, is not specifically required and the prescribing doctor need not be informed either.298 With the incentive remaining in favour of dispensing the originator brand, and the law facilitating both an originator-to-generic and generic-to-originator switch, it is likely that the use of generic venlafaxine will be limited until differences in the price are decreased and specific measures are taken to encourage generic prescribing and to counter direct to consumer advertising. It may be that additional policy measures should be implemented to minimize incentives for multiple- and reverse-switching, and prescribers, as key opinion leaders, could take the lead in promoting generics to their patients.
5.5. Further findings drawn from a collation of the four case studies

5.5.1. Impact on Expenditure

In contrast to the significant savings made in switching to generic olanzapine, opportunities to achieve further savings for the other three studied medicines were missed. Low substitution rates, a practice of initiating treatment in medicine-naïve patients with originator brand and reverse substitution from generic brand to originator were all observed, and contributed to missed opportunities for savings. Table 5.5.1 shows computed potential savings for lamotrigine and venlafaxine.

Table 5.5.1: Annual expenditure (in NZ$) for the exemplar medicines showing actual versus potential savings in the first year after reference pricing

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine 200mg/day</th>
<th>Risperidone 4mg/day</th>
<th>Olanzapine 10mg/day</th>
<th>Venlafaxine 75mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price ratio (generic : originator)</td>
<td>1.2</td>
<td>1:3</td>
<td>1:33</td>
<td>1:2</td>
</tr>
<tr>
<td>Switch rates</td>
<td>Actual</td>
<td>Potential</td>
<td>Actual</td>
<td>Actual</td>
</tr>
<tr>
<td>Annual expenditure* before</td>
<td>2,986,200</td>
<td>1,764,768</td>
<td>12,535,200</td>
<td>4,534,128</td>
</tr>
<tr>
<td>Annual expenditure* after</td>
<td>2,116,140</td>
<td>1,642,410</td>
<td>455,664</td>
<td>1,591,272</td>
</tr>
<tr>
<td>Savings* in the first year</td>
<td>870,060</td>
<td>1,343,790</td>
<td>1,309,104</td>
<td>10,943,928</td>
</tr>
</tbody>
</table>

* all values in NZ$

In the case of olanzapine, factors which facilitated high generic uptake included the significant price difference between originator and generic, and there being no prior price protection agreement in existence, and subsequent delisting of the originator brand from the Schedule and no special circumstances applicable (i.e. no Special Authority). Pressure was thus exerted on patients to switch to the generic. The consequence of this was an almost complete switch (99.7%) to either of the available generic brands and savings of around NZ$10 million in the first year.

In the case of lamotrigine and venlafaxine, however, the retention of the originator brand in the Schedule together with allowance for Special Authority approval, effectively neutralised the effect of reference pricing; switching was minimal and uptake of generics by new patients was low. Extrapolated potential savings for these medicines (see Table 5.5.1.) is lower than those achieved for olanzapine as the price ratios of generic to originator for these medicines is

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iii Calculated using the study patient numbers and prices at the time, and allowing for a 10% non-switcher rate.
significantly lower. Arguably, lower prices for generic lamotrigine and venlafaxine could have achieved, and hence also greater savings; however, as PHARMAC’s pricing negotiations often encompass multi-product agreements and are conducted under confidential conditions, no further interpretation is made.

5.5.2. Profile of a ‘switcher’ patient

Brand substitution in NZ takes place at the time of dispensing, irrespective of the brand prescribed, with the pharmacist having an obligation only to the patient in making a switch. The findings of this study suggest however, that patients are not central in this decision-making process.

No switcher profile for likelihood to switch could be identified for any study medicine. Even after combining data from the cohorts and thereby increasing the power to identify the existence of any predictors, no distinct switcher profile could be found. Amongst existing users (n=14,243), switchers (23%) were more likely to be male (OR = 1.5 [95% CI 1.4 to 1.6]) and not of Māori or Pacific ethnicity (OR = 2 [95% CI 1.7 to 2.2]); however, the included demographic indicators (gender, ethnicity, age and area of domicile) were all weak predictors of the likelihood to switch, contributing less than 10% to switch status, (correlation coefficient for each below 0.1). This is in line with findings from other studies on the weak association of patient characteristics with use of generic medicines.301

Additionally, there is evidence that patients are not offered generic alternatives. Nearly one in three pharmacies (30%) never dispensed generic venlafaxine from the date it became available in 2011 until the end of the dataset in 2014. The reasons for this behaviour are unclear; however, they are likely to be due, in part, to the mistrust of generic medicines by some pharmacists,52 and in part to financial incentives to dispense the more expensive brand (albeit a marginal (4%) proportional difference).

5.5.3. The issue of multiple switches

Although no evidence of harm exists where multiple switches were made by individual patients in this study, the practice seems undesirable from the perspective of patient safety.302

A study on therapeutic reference pricing of statins in Germany found an association of increased

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301 For example, 28 tablets of generic 75mg venlafaxine costs €4.5 (~NZ$7) ex manufacturer in Austria, 299 whilst the NZ Schedule-listed price is NZ$12 (~€ 8).282 (Similarly, 60 tablets of 100mg lamotrigine is €28 in Austria and €40 in NZ.) The median price from 16 European countries for generic venlafaxine was reported to be half that of the price in NZ. 300
hospital visits with patients who made more than one switch.\textsuperscript{131} Being able to recognise one’s medicines is a contributory factor in preventing over-dosing, as patients are at times in possession of their next dispensed prescription (their ‘repeat’) prior to finishing their previously dispensed packs. If the generic name is not used on both labels, a patient might reasonably think the medicines are different and take both at the same time. Furthermore, continued changes in the physical attributes of a particular medicine with/without labelling differences in the medicine name, can be confusing.\textsuperscript{207,303}

Multiple switches were a feature of each of the four case studies (see table 5.5.2), despite there being no apparent reason for this behaviour.

Table 5.5.2: Proportion of switchers making multiple switches by medicine

<table>
<thead>
<tr>
<th>Medicine (proportion of cohort switching at least once)</th>
<th>Single switch</th>
<th>Second switch*</th>
<th>Three or more switches*</th>
<th>No. of brands available with full subsidy following reference pricing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine (22%)</td>
<td>60%</td>
<td>30%</td>
<td>10%</td>
<td>3 generic + originator</td>
</tr>
<tr>
<td>Risperidone (75%)</td>
<td>50%</td>
<td>41%</td>
<td>9%</td>
<td>3 generic</td>
</tr>
<tr>
<td>Olanzapine (100%)</td>
<td>13%</td>
<td>86%</td>
<td>1%</td>
<td>2 generic</td>
</tr>
<tr>
<td>Venlafaxine (12%)</td>
<td>60%</td>
<td>28%</td>
<td>11%</td>
<td>1 generic + originator</td>
</tr>
</tbody>
</table>

*This could be a generic to generic switch, or generic to brand.

Factors inherent in the NZ system which might contribute to multiple switching include out-of-stock situations (although there were none for these four medicines during the study period), patient preference or mobility between different pharmacies (although this was not the case at least for venlafaxine), and the availability of multiple generic brands at community level and a difference in brand at hospital level.

In addition, reverse switching (i.e. switching from a generic to the originator brand) was also observed. Nearly 60% of new users of generic venlafaxine switched to the originator brand, and 28% of existing users made a second switch back to the originator. Reverse switching was also evident in the case of risperidone, yet occurred minimally in the olanzapine study (1.5% of cases).

5.6. Chapter Summary

This chapter presented the findings for the four medicine case studies, each with its own subtle differences in reference pricing policy implementation. Uniquely in the case of olanzapine, the originator brand was no longer subsidised following the introduction of generic equivalents, whilst for lamotrigine, risperidone and venlafaxine the originator remained funded for some time. The four medicines are used in epilepsy and mental health conditions, and reflect
conditions where brand switching might be approached tentatively by both clinicians and policy-makers.

No differences in health outcomes could be found for switchers and non-switchers, with no difference in health services or concomitant medication use. A profile for a switcher could not be identified, except for a switcher being more likely to be male and of European ethnicity. Multiple switching was observed between all available brands of the medicines.

Whilst the generic substitution policy did not result in any change in expenditure for health services use, opportunity to make further savings on expenditure on pharmaceuticals was missed in the case of lamotrigine, risperidone and venlafaxine, there being a low switcher rate for these exemplar medicines.

The role of the patient in generic substitution is explored in the next chapter, with the findings from a patient questionnaire presented as submitted for publication. Finally, a subsequent chapter (Chapter 7: Discussion) discusses the implications of the findings for the Part 1 exemplar medicines presented in this chapter together with Part 2 findings in Chapter 6: The patient’s perspective, before drawing conclusions and making recommendations in the final pages of this thesis.
Chapter 6. Part 2 – The patients’ perspective

6.1. Introduction

An epidemiological approach to measuring the impact on patients of changing medicine brand using national health datasets has its merits, yet does not give voice to patients themselves. Specifically, the datasets used in Part 1 do not provide insight into the research objectives of:

- understanding the patient’s reasoning for switching or not
- describing additional costs borne by the patients related to brand changes
- evaluating their willingness to pay for an alternative choice.

A patient survey was thus included in this research, and an article on the findings has been written and submitted for publication with a regional audience in mind. This chapter includes the main body of the article; however, in placing the study within an international context, a wider body of literature is presented in place of the submitted article’s introduction. The remainder of the chapter reproduces the journal article, with permission.

Lessing C, Ashton T, Davis PB. New Zealand patients’ understanding of brand-substitution and opinions on co-payment options for choice of medicine brand. Aust. Health Review; published online 14 September 2015.[http://dx.doi.org/10.1071/AH15004]

6.2. Abstract

Objective: This study sought to better understand the views and experiences of NZ patients on switching between brands of prescription medicines and on alternative funding options for the provision of medicines, including an increase in co-payments.

Method: A self-administered questionnaire was offered to selected patients through participating community pharmacies. Pharmacies were stratified according to level of deprivation of the community served before random selection and invitation for involvement in the study. Patient understanding of and rationale for brand substitution was assessed. Preference for different co-payment options was elicited, together with demographic and other explanatory information.

Findings: A total of 194 patient-completed questionnaires were returned. Some gaps in patient knowledge and understanding of brand changes exist. Most respondents indicated a preference for the existing subsidy arrangements with little desire expressed for alternatives.
Around half were willing to contribute towards paying for a choice of brand other than the subsidised brand; however, the maximum contribution nominated was disproportionately lower than real cost differences between originator brand and generics.

Conclusion: Some work has been done to inform the public on substitution policies. There may be some additional gain in ensuring that New Zealanders are aware of the full cost of their medicines.

6.3. Introduction & review of the literature

Although generic medicines have been available since the 1920s with the promotion of different brands of aspirin, requirements for the registration of generic medicines by the FDA through the Hatch-Waxman Act were formalised in 1984. NZ patients have had a long relationship with generic medicines dating from the 1990s, and three quarters of medicines dispensed are generic brands.9,38 Substitution by pharmacists of the prescribed brand with that of the Schedule listed brand is enacted in NZ law, and pharmacists are expected to dispense the Schedule-listed brand, most often the generic equivalent of an originator brand, without having to consult the prescribing doctor.298 Patients and doctors in NZ can veto substitution of their prescribed brand; however, such a veto will most often result in the patient having to meet the full cost of the prescription, and this amount can be considerable; (e.g. the price of originator brand of olanzapine is 50 times that of the Schedule-listed generic brand).382

Limited studies have been conducted in the NZ setting evaluating opinions on generic medicines or brand switching. In a 2003 NZ study patients reported that their doctors either did not offer opinions on brand changes or were passive in their comments regarding prices of medicines.108 These patients also reported a reluctance to change brands being due to satisfaction with the existing medicine rather than a concern over the substitute.108 Some NZ pharmacists and doctors reported a distrust of the efficacy of generic medicines in surveys,27,52 whilst NZ consumers have stated they are more likely to use generic medicines for less serious illnesses or if recommended by a pharmacist or their doctor.51,108

Suspicion regarding generic medicines and substitution however, persists in NZ amongst some patients and health professionals,27,51,52 and may have been heightened following more recent and highly publicised brand changes to levothyroxine and omeprazole.54,305 This distrust of generics in NZ is potentially fuelled by pharmaceutical company strategies such as direct-to-consumer advertising of prescription medicines, pharmaceutical company sponsorship of some NZ patient health organisations and product-detailing to doctors.306 However, the surveys conducted in NZ have also found a lack of knowledge regarding generic medicines amongst
consumers and health professionals alike, with the majority (80%) of doctors in one survey (n=173) unable to distinguish originator from generic brand names when presented with a list of 12 medicine names.171 (Thus discussions perhaps should focus on changing between brands rather than on change to generic medicines per se.)

Reviews of studies conducted internationally on opinions of generic medicines and brand preferences coalesce on the extent of brand loyalty and distrust of generics being around 30%-40% of survey respondents,97,98 (including reports from Spain 13%,28 USA 23%,307 Poland 21%,308 Australia 46%306). Amongst patients expressing reluctance to use a generic or different brand medicine, certain patient features are variably reported to have a relationship with preference. Whilst age, education level, and source of information appear to influence preference in some countries, in other studies these variables show no association.97,98 A study in Denmark noted that unobserved (unmeasured) patient characteristics accounted for 27% of variation in brand choice.310 Consistent in the studies, however, is the influence of perceived disease severity on brand preference, with use of generic medicines more acceptable in conditions considered less severe.51,75,98,105,311-314.

Consistent also is the regard in which patients hold the attitude of health professionals towards generic medicines or brand changes.97,98 Attitudes of doctors and pharmacists thus have relevance to the discussion. Whilst pharmacists in Sweden and some doctors in the US,99,100 generally agree that generics are better value for money, other doctors in the US and Ireland report they would rather not use generics themselves.101,102,103 Health professionals in Sweden, Ireland, Finland, and Italy raise the issue of creating confusion amongst patients through changing medicine brands.99,102,104,105,26 Australian pharmacists reported that offering substitutions can be professionally challenging and results in patient confusions and annoyance.102 Key demographic features of the prescribers and pharmacists, such as age, show no clear association with attitudes. However, private doctors in Sweden are reported to be more likely to veto substitution over salaried doctors,315 as were Swiss hospital-based doctors than general practitioners or specialists.313 Individually-owned pharmacies in the Netherlands were reported to be more likely to reverse-substitute (changing a generic to an originator brand) over pharmacy chains,312 and in the US substitution occurs more frequently under Medicaid than under private third party or indemnity insurance systems.316

Payment for brand choice is a cost-sharing strategy employed by many countries, although the form may differ.317 Citizens in Switzerland are unwilling to pay anything extra for branded medicines over generics,318 and consumers in Finland consider price, familiarity and availability more important than physical characteristics of the medicine when considering substitution choice.319 A US-based study found 30% of patients with chronic gout were unwilling to make
extra monthly payments for a cure, with those willing to pay being younger and experiencing more frequent attacks. A meta-analysis of the effects of co-payment within US public insurance systems on adherence to prescription treatment found increased odds of non-adherence where co-payments are required, with flow-on effects of greater use of other more expensive medical services. Use of co-payments are also known to enhance ethnic disparities: Māori and Pacific peoples in NZ were noted to be more likely to defer collection of prescription items because they could not afford the prescription costs, and similar findings on ethnic disparity were reported in a study comparing seven countries including NZ, Australia and Canada. Another option of private insurance, mooted to participants in a NZ survey, was accepted by a majority (61%) to have the potential to increase accessibility or affordability of medicines which they perceived they might need later on in life for conditions such as cancer, yet only half would be willing to take up private insurance and would contribute NZ$20 or less per year for the perceived benefit.

Overall, it appears that around one in three patients express a desire to use a particular brand (largely the originator brand over generic equivalents), especially in conditions perceived to be more serious, yet do not appear to accord particular value to a brand itself, rather to the option of choice, and find increased co-payments for exerting that choice unacceptable. This study thus sought to explore patients’ perspectives on alternative funding mechanisms, in addition to understanding their perception of generic medicines and brand switching.

6.4. Method

This study employed a questionnaire delivered to selected NZ patients attending a pharmacy. The study was approved by University of Auckland Human Participant Ethics Committee.

6.4.1. Study sample

Recruitment of patients to participate in the study was undertaken by community-based pharmacists, who themselves were identified from the register of New Zealand community pharmacies. The list of 938 community pharmacies was stratified by level of deprivation of the population they served, (using a modified NZDep index) before random sampling within each stratum was conducted. The NZDep is a 10-point scale, with an index of 10 indicating the area is lived in by the least socially and materially well-off people. The ten-point scale was collapsed into three strata. Sampling aimed to capture 10% of pharmacies within each stratum and to achieve a pharmacy sample size of 100. Pharmacies were selected in groups for medicines from
three therapeutic categories, these being lamotrigine, a calcium channel antagonist or a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor.

Pharmacies were contacted in the first instance by a letter, and later followed up with a reminder telephone call. Pharmacists were given instructions on how to randomly select up to 20 patients (both those who had and hadn’t changed brands) from their database, and invite them to complete a questionnaire whilst in the pharmacy. Patients were recruited during the period April to August 2013.

6.4.2. Survey instrument

In-depth interviews with 7 patients, together with findings from other NZ-based surveys, were used to inform the development of a draft questionnaire. Interviewees were recruited by convenience sampling and interviews conducted until saturation of themes (seven participants). Pilot testing at two community pharmacies and subsequent modifications led to the final questionnaire used in this study.

The questionnaire was designed to be self-administered, rapidly completed (patients were expected to complete the questionnaire whilst waiting for a prescription to be filled) and anonymous.

Using multiple-choice and checkbox options, patients’ knowledge on which brand of medicine they were currently taking, and how many times that particular brand had been substituted, was assessed, as well as their understanding of and rationale for brand substitution. Three versions of the questionnaire were printed, specifically using the names of the medicines used to invite the patient to participate; i.e. Question 1 asked the patient which brand of medicine they were taking, and listed the possible options for them to select.

Five-point Likert scale responses (from strongly agree to strongly disagree) were used to elicit patients’ preferences for different co-payment options in general and related to substitution, including a question specifically asking the respondent to nominate a dollar value they would be prepared to pay for their choice of medicine brand.

Demographics of the patients were also sought as well as other explanatory variables, including level of education, income, number of concomitant medicines taken, experience of medicine related adverse reaction, self-reported disease severity, and primary source of substitution information. Education and income scales were based on the NZ census data to enable comparison. (A sample questionnaire is attached as Appendix 1 at the end of this thesis.)
6.4.3. **Data analysis**

Questionnaire data were first entered into Microsoft Excel (Microsoft Corporation, Redmond, USA) for examination, coding and cleaning and then exported to SPSS Statistics (Ver. 21 IBM Software New York, USA) for analysis. Descriptive statistics were employed to document frequency and percentage. Logistic regression was used to determine any association between explanatory variables (age, gender, education and income) and the responses.

6.5. **Results:**

Thirty three pharmacies returned questionnaires (i.e. response rate 33%), almost half of whom (45%) were located in areas of most deprivation. In all, 194 patients participated [mean (s.d.) number of respondents per pharmacy 6±4; range 1–19].

**Table 6.1: Key characteristics of respondents**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>61.1 (+14.3)</td>
</tr>
<tr>
<td>Mode age group, years</td>
<td>70 to 74</td>
</tr>
<tr>
<td>Proportion 65 year and older</td>
<td>45%</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>47.3%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>86.2%</td>
</tr>
<tr>
<td>Māori or Pacifica ethnicity</td>
<td>8.6%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.1%</td>
</tr>
<tr>
<td>Other</td>
<td>4.1%</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>1.7%</td>
</tr>
<tr>
<td>Secondary</td>
<td>47.2%</td>
</tr>
<tr>
<td>Trade qualification</td>
<td>17.4%</td>
</tr>
<tr>
<td>University</td>
<td>33.7%</td>
</tr>
<tr>
<td>Net annual income</td>
<td></td>
</tr>
<tr>
<td>&lt;NZ$15,000</td>
<td>6.4%</td>
</tr>
<tr>
<td>NZ$15-30,000</td>
<td>24.4%</td>
</tr>
<tr>
<td>NZ$30-50,000</td>
<td>28.8%</td>
</tr>
<tr>
<td>NZ$50-70,000</td>
<td>18.6%</td>
</tr>
<tr>
<td>NZ$70-100,000</td>
<td>10.3%</td>
</tr>
<tr>
<td>&gt;NZ$100,000</td>
<td>11.5%</td>
</tr>
</tbody>
</table>
6.5.1. Characteristics of respondents

Completed questionnaires were received from 194 patients, whose characteristics are detailed in Table 6.1. Respondents were almost equally split into males and females, 45% of whom were over the age of 65 years, and the cohort was largely of European ethnicity. Respondents had a higher than average level of education and income than the 2013 NZ population.8

One third of respondents indicated they had experienced an adverse reaction to a medicine, whilst a further 10% had witnessed a reaction in a family member. On a scale of 1 to 6 (from unnecessary to life-saving) most respondents scored their medicine as not life-saving but somewhat important (mode of 4). No respondent considered their medicine unnecessary, whilst approximately 20% considered it life-saving. Respondents consumed a monthly average of 4 medicines.

6.5.2. Experience of brand-substitution

Respondents equally indicated that their first source of information on brand substitution was from either a doctor or pharmacist (35% each). 17% said they had never heard of brand substitution and 9% had heard about the subject via TV or radio. When presented with a list of relevant brand names, most respondents could identify which brand of medicine they were currently taking; only 6% could not.

Slightly more than half of respondents (58%) indicated they had experienced brand substitution at least once. The only patient characteristic correlated to whether patients identified as having changed brands or not was age, whereby younger patients were more likely to have changed brands (p=0.004, Pearson’s correlation = 0.21). Most patients stayed on the medicine they had changed to, with only 7% indicating they had made a change back to the previous brand (see Table 6.2). The majority (64%) indicated that they continued using the brand to which they had been switched as they had no problems with the change. A further 13% continued using it as they felt that the substitution had been explained to their satisfaction, whilst 10% didn’t know they had a choice to switch back and 14% indicated they could not afford to pay for the alternative.

Of the 42% of respondents who stated they had never changed brands, the majority (61%) did not know they could change (see Table 6.2). Six percent indicated that it was their right to choose not to change, whilst 4% had been influenced by the radio or TV. A further 2% had an adverse reaction in the past, could afford to pay for their choice (2%) or had ‘other’ (undefined) reasons for not changing (25%).
The questionnaire also asked respondents to indicate if they had incurred any extra costs due to brand-substitution: few respondents (7%) indicated that they had.

### Table 6.2: Participants reasons for changing brands or not changing

<table>
<thead>
<tr>
<th>Changed brands at least once and continued using the next brand (n=113; 58%), because:*</th>
<th>Never changed brands (n=81; 42%), because:*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Had no problems with the new brand (64%)</td>
<td>• Didn’t know had a choice (61%)</td>
</tr>
<tr>
<td>• Can’t afford to pay for the original brand (14%)</td>
<td>• Choice is a right (6%)</td>
</tr>
<tr>
<td>• Substitution explained satisfactorily (13%)</td>
<td>• Influenced by media (4%)</td>
</tr>
<tr>
<td>• Didn’t know had a choice (10%)</td>
<td>• Previous bad experience (2%)</td>
</tr>
<tr>
<td></td>
<td>• Can afford to pay for the original brand (2%)</td>
</tr>
<tr>
<td></td>
<td>• Other (25%)</td>
</tr>
</tbody>
</table>

* Respondents could choose as many answers as applied

### 6.5.3. Opinions on payment for medicines

Regarding subsidy for medicines in general, 45% of respondents stated that all medicines should be free for everyone (see Table 6.3). There was almost complete agreement (97%) that certain categories of people should receive their medicines free of charge (such as the elderly and children). A third of respondents felt that people who could afford it should pay the whole amount for their medicines. One quarter of respondents agreed that they should pay a percentage of the cost of the medicines rather than the current flat NZ$5 fee, and 73% felt medicines should be paid for by taxes and not private health insurance.

Most respondents (65%) felt they should not have to change brands, with 51% stating they should not have to pay for choosing a brand different to the fully-funded brand (see Table 6.3). Almost all (97%) felt they should be able to change back at no charge if the new brand didn’t suit them.

### Table 6.3: Responses to questions on medicines’ funding and substitution policies

<table>
<thead>
<tr>
<th>Statement</th>
<th>In agreement</th>
<th>Unsure/ Neutral</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>All medicines should be free of charge for everyone</td>
<td>45%</td>
<td>3%</td>
<td>52%</td>
</tr>
<tr>
<td>Certain medicines should be free of charge for everyone</td>
<td>80%</td>
<td>1%</td>
<td>19%</td>
</tr>
<tr>
<td>Medicines for certain people should be free of charge (for e.g. elderly, children, other)</td>
<td>94%</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>People who can afford it, should pay the whole amount for their medicines</td>
<td>30%</td>
<td>3%</td>
<td>67%</td>
</tr>
<tr>
<td>Everyone should pay a percent of the cost of their medicines, and not just the $5</td>
<td>25%</td>
<td>4%</td>
<td>71%</td>
</tr>
<tr>
<td>Medicines should be paid for by private health insurance not taxes</td>
<td>22%</td>
<td>5%</td>
<td>73%</td>
</tr>
<tr>
<td>If I choose a medicine different to the fully funded one, I must pay for it</td>
<td>41%</td>
<td>8%</td>
<td>51%</td>
</tr>
<tr>
<td>If the new medicine doesn’t suit me, I must be able to change back at no extra charge</td>
<td>97%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>I shouldn’t have to change</td>
<td>65%</td>
<td>20%</td>
<td>15%</td>
</tr>
</tbody>
</table>
No relationship could be found between the patients’ identified brand change status (had they experienced a brand change or not) and their responses on payment options.

In response to being asked to nominate an amount they would pay for choice of brand, almost half of the respondents stated they were unwilling to pay anything extra for choice (49%), whilst 5% stated that there was no limit on what they would pay; see Figure 6.1. The amount patients were willing to contribute was correlated with their stated income (p=0.01; Pearson’s r=0.22) and number of medicines concurrently being taken (p=0.03; r= -0.2), with other explanatory variables having no influence. In conflict, however, 24% of those who agreed with the statement “If I choose a medicine different to the fully funded one, I must pay for it” also indicated they were unwilling to pay anything extra for that choice.

Figure 6.1: Responses to survey question on co-payment for choice

<table>
<thead>
<tr>
<th>Amount</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nothing extra</td>
<td>60</td>
</tr>
<tr>
<td>NZ$5</td>
<td>50</td>
</tr>
<tr>
<td>NZ$10</td>
<td>40</td>
</tr>
<tr>
<td>NZ$20</td>
<td>30</td>
</tr>
<tr>
<td>NZ$35</td>
<td>20</td>
</tr>
<tr>
<td>NZ$50</td>
<td>10</td>
</tr>
<tr>
<td>There is no limit</td>
<td>5</td>
</tr>
</tbody>
</table>

"To be able to choose which brand of medicine I take, I am willing to pay…”

6.6. Discussion

6.6.1. Patient understanding of brand substitution:

All patients in this study were taking a medicine which had been affected by a brand change. Only a minority (n = 11; 7%) reported ever changing back to a previous brand, with the majority of respondents expressing no problems with the substituted brand.

A lack of knowledge of substitution as an option was, however, apparent amongst some. Two-thirds of those who stated they had not changed brands indicated that they did not know
they could change. Of those who had made a change, 1 in 10 did not know they had the option to change back, and of all respondents, 17% had never heard of brand substitution, although this might also include new patients initiated on the latest subsidised brand.

Considering their pivotal role, and as confirmed by this study’s respondents, prescribers and pharmacists are the primary source of information on substitution, and their attitudes towards brand substitution are likely to be paramount. Findings from international settings suggest pharmacists feel challenged in having to explain the regulatory and economic aspects of substitution to patients rather than being able to focus on clinical issues, and this might be a contributory factor in NZ also.102,323

PHARMAC has responded to uncertainty around switching and has undertaken several activities to increase awareness of brand changes. A leaflet explaining brand switches (“My medicine looks different”) is distributed to patients through NZ pharmacies and medical practices and was available before this study was undertaken. Patient-specific literature is available on the PHARMAC website. In addition, educational meetings have been held to assist pharmacists in explaining changes of medicines for mental health conditions, and pharmacists are reimbursed per patient for the additional time they need to counsel patients on product specific changes (called a ‘brand switch fee’). Despite PHARMAC’s efforts to inform consumers, a lack of knowledge amongst this study’s patients persisted.

6.6.2. Patients’ opinion on payment for brand choice:

Most respondents indicated a preference for the existing subsidy arrangements with little desire expressed for alternative systems such as paying a proportion of the medicines’ cost. Half the NZ respondents agreed they should pay for requesting a brand other than the subsidised one.

Responses to such questions are likely to be influenced by country-specific reimbursement policies and acceptance of generic medicines. In Switzerland, where patients pay a portion of the cost of their medicines, 30% of citizens were willing to pay for a branded medicine over a generic.318 Yet, although generic substitution was permitted in 2001 in Switzerland, generic penetration in the Swiss market is low (21% by volume in 2011) in comparison with New Zealand (73%).9

With regard to how much respondents were willing to pay for choice of brand, only 13% of respondents in this study were willing to pay at least NZ$20 (~US$15) per month, an amount considerably less than the difference in price between most originator and generic brands used for patient selection in this study (either lamotrigine, a calcium channel antagonist, or a HMG-CoA reductase inhibitor). In other words, although half the respondents were willing to pay for
choice, the amount they would contribute was poorly aligned with true originator-generic cost differences, and additionally was positively correlated with stated income. That only 15% of respondents accepted the need for brand substitution further suggests a lack of knowledge of the price differences in generics versus originator brands and of PHARMAC pricing mechanisms.

It is possible that NZ patients are unaware of the true cost of their medicines. A feature of the NZ dispensary IT systems in the past detailed the cost of a medicine with a breakdown of patient and government contributions. This has however, been removed and receipts now only indicate the fixed co-payment amount per item (NZ$5 for a 3 month supply). In addition, in certain cases patients are shielded from paying the full price of their medicines via a Special Authority (SA) arrangement. When new and expensive products are introduced into the Schedule for the first time, prescriptions often require an SA for prescription. Such a mechanism is intended to control the prescribing rate until experience with the new medicine has been gained and/or the cost is lowered by the supplier. If a patient has been granted an SA number they will continue to receive that brand of a medicine for the duration of their SA (usually granted for a minimum of 2 years and is renewable), irrespective of whether a less expensive generic version is available. Throughout the SA period NZ patients only pay the fixed co-payment fee.

6.6.3. Limitations of the study

The study relied on patients being identified and recruited by pharmacists, with the questionnaire delivered within that patient’s pharmacy. The response rate from pharmacists willing to participate was low (33%). Pharmacists felt over-surveyed in some instances or that the administrative burden of recruiting patients was too great. Pharmacists were given detailed implementation instructions, and methods were described to ensure patients had the opportunity to decline participation in the first instance and could answer the anonymous questionnaire without influence or coercion.

However, how well this was implemented is unknown. Not all pharmacists complied with the protocol instructions, in that some allowed patients to take the questionnaire home (and consequently these were not returned), or did not record the number of patients to whom they offered it, or who declined to participate, making calculations on extent of patient participation unfeasible. In addition, pilot testing of potential answers to questions 1 and 2 of the questionnaire, compounded by poor patient selection, did not reveal the limitations of these questions. Pharmacists were to identify switcher and non-switcher patients, and give them the appropriate questionnaire. The data from question 1 was not used in the analysis.
Respondents were all adult patients who may, or may not, have been responsible for the payment of medicines in the household. The questionnaire did not elicit this information and so, in some cases, the response on medicines’ payment options might be different for patients from that of the payer.

Anecdotally, a language barrier existed. One pharmacist commented that his patients were mostly non-English speakers, and that had he participated, he would have had to translate the questionnaire for them. The demographics of respondents in this study show an underrepresentation of people of Asian ethnicity (1% in this study versus 9% in the 2013 census). Māori and Pacific peoples were also slightly underrepresented (9% vs. 15% respectively) and Europeans over-represented (86% vs. 59%). The questionnaire had been pilot-tested in a low-middle income suburban pharmacy and one of mixed income, but did not specifically seek out people speaking English as a second language.

Although an attempt was made to attain a representative sample of respondents, 45% of pharmacies who agreed to participate were situated in areas of lower socioeconomic status, yet respondents had higher than average levels of education and income than the 2013 NZ population. Thus, extrapolation of the findings to the entire NZ population has certain limitations.

6.7. Conclusion

Acceptability of brand substitution relies on patients understanding the reasons for the change. This study suggests that although most patients have experienced brand changes without any problems occurring, a lack of knowledge about substitution does persist.

Additionally, although half the respondents indicated willingness to contribute towards paying for choice of brand other than the Schedule-listed brand, the dollar value they would contribute is lower than the true cost difference between the two.

Work has already been done by PHARMAC in educating the public around substitution policies, and experience over time has probably contributed further to a general acceptance and understanding of brand changes. There may be some additional gain in ensuring that New Zealanders are aware of the full cost of their medicines, not just of the co-payment fee, at the point of dispensing.
6.8. Chapter summary

This chapter presents the nested Part 2 study largely as submitted for publication. It provides both the viewpoint of the NZ patient as well as some insight into a patient’s involvement in the decision making process regarding changing medicine brands. The findings hint at patients holding a peripheral role, and underscore a lack of in-depth understanding of the cost of medicines and the processes PHARMAC undertakes to ensure their provision.

Chapter 7 integrates the findings of the 4 case studies from Part 1 with the findings from this chapter in an overall discussion, and reflects on the research question, before drawing some conclusions for this thesis.
Chapter 7. Discussion, Recommendations and Conclusion

This chapter discusses the findings of the four case studies (Part 1) and questionnaire (Part 2) in light of the current pharmaceutical system in NZ, highlighting potential weaknesses within the existing practices and policies. Implications for current policy, as well as opportunity for savings to be made in the immediate future, and potential research areas are also discussed.

7.1. Reflecting on the study hypotheses

7.1.1. No adverse health outcomes result from switching brands

Available literature on the effect of reference pricing on health outcomes to date has been weak, restricted both in the low number of studies conducted and their generalisability.\textsuperscript{31,90} Four studies conducted amongst a select Canadian population\textsuperscript{135,143,199,324} and one German study\textsuperscript{131} are available to draw evidence from, all of which reported no adverse effects of reference pricing on health or healthcare utilisation.\textsuperscript{10,31,111,325,326} However, study design limitations exist, with an updated Cochrane review excluding the four Canadian studies on the basis that they are cost-benefit analyses and do not meet methodological inclusion criteria of at least two intervention and two control sites.\textsuperscript{90}

The conditions required to employ a natural experiment to study effects of reference pricing policies exist in New Zealand: an intervention (the policy), which is outside of the control of the researcher, is enacted on a discrete population (the users of a particular medicine), at a single point in time (a change in the Schedule-listed brand).

A difference-in-differences methodology, with paired, individual patient data, comparing the before-after differences of switchers with that of non-switchers, was adopted. This technique attends to the potential bias due to a lack of randomisation, and is marginally stronger than a ‘triangle design’ (post versus pre versus control) which does not account for temporal or other influences on the control arm. Prior to the four case studies presented in this thesis, only one difference-in-differences study examining health outcomes of reference pricing had been published.\textsuperscript{131}

Using such a difference-in-differences estimate of treatment effect, the case studies included in this thesis found no difference in rates of mortality, use of secondary level health services, or consumption of adjunctive medicines amongst patients who switched brands compared with patients who did not switch. It is this absence of effect, determined under conditions of a series of natural experiments, which allow the causal inference to be made that
reference pricing and consequent brand substitution of at least these four originator brand medicines to their generic equivalents is clinically justified.

An examination of the findings however, revealed multiple- and reverse-switching; an unanticipated effect of policy implementation, which might have clinical consequences. Furthermore, although the case studies were able to establish that no change in prescribing occurred as a result of generic substitution, no account of the instances where patients sought reassurance from health practitioners could be made.

7.1.2. The likelihood of a patient to switch can be predicted

_The decision to switch_

No ‘switcher profile’ could be defined, there being no ‘likelihood to switch’ attributes identifiable. Additionally, this thesis found that a significant number\(^\gamma\) of patients reported that they did not know they could choose to switch (or not), that multiple switching between brands was evident, and that some pharmacies did not offer a choice, stocking only a single (originator) brand.

Substituting the dispensed brand of medicine from that which has been prescribed to a generic equivalent by a pharmacist is enacted in NZ law. Aside from bioequivalence, the conditions under which this can be done include that there is no clinical reason not to do so, that the prescriber has not endorsed the prescription prohibiting it, and that “the pharmacist informs the patient of the brand substitution”.\(^{298}\) The findings of this study affirm that, indeed there are no clinical reasons to prohibit substitution, and suggest that the decision to switch brands is made primarily by the pharmacist and to a lesser extent the patient.

_Rights and responsibilities_

The responses of patients in the questionnaire-based study suggest a disconnect between expectations for the right to choose and an understanding of the implications of exerting this choice in favour of the more expensive originator brand. Half of the respondents indicated willingness to pay for having a choice in brands, yet the amounts proposed were not realistic in terms of the cost differences between originator and generic brands. There appears to be little understanding of the cost implications if generic reference pricing and substitution policies are not implemented.

\(^{\gamma}\) 61% of patients who stated they had not switched brands indicated that they did not know they could.
The pharmaceutical industry, through the media, actively educates patients on ways to exercise their brand choice, yet there is little apparent activity in educating the New Zealand public either on funding mechanisms or on generic equivalence of medicines.

At the individual level, legislation places the responsibility on the pharmacist for informing patients on substitution when making a change; however, there is no imperative for the pharmacist to initiate generic substitution in the first place. In contrast, in Germany, doctors are legally required to explain to their patients why they deem a surcharged product necessary, and pharmacists are legally required to substitute to the generic or less expensive parallel imported brand.87 Unless NZ pharmacists are convinced of the clinical equivalence of generic medicines and are not financially compromised when making a substitution, they will experience conflict in fulfilling their responsibilities. Incentivising pharmacists may be integral to increasing uptake of the preferred, less-expensive generic brand, as well as in educating patients about their rights and responsibilities regarding choice.

7.1.3. The economics of switching

The third hypothesis tested was that the cost of any difference in health service utilisation between ‘switcher’ patients and ‘non-switchers’ is offset by the economic benefit of reference pricing. Accepting the limitation of a lack of data from the community provider level, no additional resource utilisation was found for patients switching to generic medicines in this thesis. Whereas savings were maximised in generic reference pricing of olanzapine, low switch rates in the case of lamotrigine, risperidone and venlafaxine resulted in missed opportunity for greater savings. Areas where implementation of the policy could be strengthened include creating incentives for pharmacists and removing the disabling Special Authority policy and the practise of funding multiple brands.

*Incentives for pharmacists*

In an analysis of European interventions to enhance the uptake of generic medicines, the issue of price neutrality has been raised; i.e. that it should not be disadvantageous for pharmacists to dispense generics.75,83 The sustained funding of differentially priced originator and generic brands by PHARMAC remains in place, for not only the study medicines, but for other medicines in the Schedule. A marginal percentage profit is achieved by pharmacies in dispensing the originator brand over the generic; i.e. there is a lack of price neutrality. Over time, years even, the agreed subsidy of the originator brand does achieve a neutral point with that of the generic equivalent. However, it would be economically more advantageous to have a rapid,
complete switch of all patients to the less-expensive generic, rather than adopting this gradual approach.

The payment of a ‘Brand Switch Fee’ paid to pharmacies for each patient switched to the preferred brand (see Chapter 3) might be considered as an incentive for pharmacists to encourage switching. However, as a one-off fee, this is still less than the marginal profit made in dispensing the more costly original brand, and whilst both brands remain funded, is unlikely to achieve greater, faster generic uptake. Furthermore, for pharmacies using automated (‘robotic’) dispensing systems, additional costs are incurred in changing brands due to the need to purchase brand-specific canisters used in the dispensing machines. Additional considerations for a pharmacy owner are the logistics of maintaining more than one brand of a medicine (shelf-space, ensuring uninterrupted supply, expiry of stock) and the risk of being left with excess (unfunded) stock, although PHARMAC does give lengthy notice of upcoming changes.

In July 2012, a step was taken towards changing the funding model for pharmacies from a fee-for-service system to a capitation model, and discussions are ongoing regarding models for reimbursements to pharmacies. Selected patients, meeting stipulated criteria, who require close monitoring, can be enrolled with their chosen pharmacy. In turn, the pharmacy is contracted by the parent DHB to provide services which include monitoring and advice giving, but also the dispensing of individually packed dosages (e.g. ‘blister packing’) at frequencies that met the patient’s needs (daily, weekly or monthly). The capitation-like fee for these services paid by the DHB to the pharmacy removes the repeated cost to the DHB associated with multiple dispensings that are often therapeutically necessitated. However, as the model does not include the cost of the medicines, brand specific reimbursement is maintained, and thus the opportunity to incentivise pharmacists to make substitutions is absent.

Special Authority – a disabling force

Despite generic reference pricing being applied, the originator brand remained fully funded to patients on condition of a valid SA approval (given for a 2 year period and renewable, see Chapter 3), for the exemplar medicines in this thesis, except for olanzapine. No incentive for patients or pharmacists existed to promote switching, and no policy was in place to promote generic uptake by prescribers or new patients. Indeed, no policy exists on commencing therapy with any particular brand other than using Schedule-listed brands. Where the originator brand remains funded, passive uptake of the generic brand appears to be low, (only 5% of venlafaxine-naïve patients started therapy with generic venlafaxine) and reverse switching is facilitated (switching from generic to originator brand).
It is not strictly the uptake of generic medicines that is at issue. Indeed, if the price of the originator brand were equal to a generic brand, uptake of the generic brand would be no more desirable than use of the originator. The issue relates to the price differential between fully funded originators and generics as existed at the time of the study (see Table 5.5.1). It is the Special Authority policy which disables generic uptake by facilitating preferential use of the more expensive originator brand. When access to a medicine has been widened due to availability of less expensive generic equivalents, Special Authority restrictions serve only to provide brand-specific access and should be removed. Higher uptake of less expensive brands will achieve greater savings to the community pharmaceutical budget overall.

Multiple brands and sole-supply status

An examination of the four study medicines highlighted a feature of multiple brands being available: in the case of risperidone, three generic brands as well as the originator brand were all listed\(^4\) (and funded) and, similarly for both olanzapine and lamotrigine, two generic brands were funded (see Table 5.5.2).

Aside from the observation that a significant portion of patients made multiple switches between brands, and that stocking a number of brands of one medicine is not ideal for the pharmacy owner, the funding of multiple brands raises questions regarding the efficiency of PHARMAC in achieving the lowest possible prices. The leverage PHARMAC has in offering the entire NZ market to one company (sole-supplier status) is greater than the sum of the parts in offering portions of the market to a number of suppliers.

In the case of venlafaxine and lamotrigine, large price differentials between originator and generic brands were sustained over a period of years with PHARMAC apparently slow to take advantage of lower generic prices. Price protection remained in place, multiple brands were listed in the Schedule and the agreed subsidy for generic lamotrigine, for example, remains higher than that in Australia (2015),\(^{328}\) and for venlafaxine, higher than in 13 EU countries (2012).\(^{300}\)

Conceivably, even lower prices could be achieved for generic medicines if price protection is not offered to suppliers of originator brands and the benefits of sole-supplier status is maximised. Recognising however, that for commercial reasons PHARMAC’s purchasing methods of tendering, negotiating and cross-product agreements are conducted in confidence, there are limits to any discussion on prices of individual medicines. Indeed, PHARMAC reports that it has

\(^{4}\) Only one brand of risperidone tablet in available in the April 2015 Schedule. This is a different generic brand to the previously listed 4 brands, and a Brand Switch Fee applies.63
saved NZ$600 million between 1997 and 2015, or around NZ$30 million per year in purchasing
generic products in this way.\textsuperscript{43,329} The knowledge that no negative effects on health could be
found for generic substitution, removes any argument for sustaining the supply of originator
brands, and thus the findings presented in this thesis may serve to strengthen PHARMAC’s hand
in price negotiations.

\textbf{Opportunity for savings in the next 5 years}

The resources available to fund medicines are not limitless: New Zealand’s tax-derived
pharmaceutical budget is set (and capped) annually and PHARMAC must make decisions on how
to best spend the available funds. As patents expire and generic equivalents become available
opportunity is presented to make savings to the overall pharmaceutical budget. In turn, these
savings translate into opportunities to widen access to existing medicines or to add new entities
to the list of funded medicines.

The pharmaceutical marketplace is arguably becoming more complex, with a shift towards
biologically-derived pharmaceuticals. Examples of such biopharmaceuticals (or ‘biologicals’)
include vaccines, but now also include hormones such as certain insulins and interferons which
are more complex molecules often targeting specific receptor sites in the body. These
biopharmaceuticals are considerably more expensive than traditional pharmaceutical products
and funding them within a capped budget will be challenging.\textsuperscript{330} Although the first generic
equivalents of biopharmaceuticals have been launched into the market, most regulatory
authorities regard ‘biosimilars’ with more caution than traditional generic medicines, and
requirements for their registration are more stringent than for generic medicines.\textsuperscript{331} Evidence of
equivalence of biosimilars is set at higher standards than generic medicines, in that clinical trials
of effectiveness are generally required.\textsuperscript{331,332} Hence the opportunity for economic gain may be
slower and less dramatic for these expensive products than for chemically-derived generic
medicines.

Of the top 20 medicines by cost dispensed in NZ in 2014 (see Table 7.1),\textsuperscript{165} patents have
recently expired for 11 and a further 7 patents will expire by 2020. Thus opportunity may\textsuperscript{vii} soon
exist to fund generic or biosimilar versions of most of the pharmaceuticals on this list which
currently account for the greatest proportion of annual expenditure.

Examining the pharmaceuticals on the list raises some issues relating to brand switching.
Most of the preparations are biologicals, for which PHARMAC notes that expenditure is
increasing rapidly and is “unsustainable”.\textsuperscript{333} Over a 5 year period expenditure for biologicals

\textsuperscript{vii} Pending any patent extension applications by the originators.
increased by 48% compared with 5% for all other medicines over the same period. Availability of the less expensive biosimilars has allowed PHARMAC to fund imatinib in 2014, and to institute a brand switch for erythropoietin alpha. Acceptability of biosimilar substitution amongst doctors, pharmacist and patients is yet to be tested: the standards for bioequivalence might satisfy users, or the severity of the conditions for which they are used may challenge any substitution policy. A study in Belgium has examined attitudes towards biosimilars amongst clinicians and reports a lack of certainty regarding interchangeability.

Table 7.1: Patent status of the top 20 medicines funded in 2014 in NZ (annual expenditure by ex-manufacturer price)

<table>
<thead>
<tr>
<th>Rank*</th>
<th>Medicine/Product</th>
<th>Patent expired</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adalimumab (biological)</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Trastuzumab (biological)</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Dabigatran</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Fluticasone with salmeterol (inhaler)</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Budesonide with eformoterol (inhaler)</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Etanercept (biological)</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Imatinib mesilate (biological)</td>
<td>Yes (already funded)</td>
</tr>
<tr>
<td>8</td>
<td>Insulin glargine (biological)</td>
<td>No (due 2016)</td>
</tr>
<tr>
<td>9</td>
<td>Rituzimab (biological)</td>
<td>No (due 2016)</td>
</tr>
<tr>
<td>10</td>
<td>Bortezomib (biological)</td>
<td>No (due 2017)</td>
</tr>
<tr>
<td>11</td>
<td>Tiotropium bromide</td>
<td>No (due 2021)</td>
</tr>
<tr>
<td>12</td>
<td>Risperidone</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>Blood glucose diagnostic test strip</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Pneumococcal vaccine</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>Sodium valproate</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>Efavirenz with emtricitabine and tenofovir disoproxil</td>
<td>No (due 2020)</td>
</tr>
<tr>
<td>17</td>
<td>Venlafaxine</td>
<td>Yes</td>
</tr>
<tr>
<td>18</td>
<td>Octreotide (biological)</td>
<td>No (due 2017)</td>
</tr>
<tr>
<td>19</td>
<td>Erythropoietin (biological)</td>
<td>Yes (already funded)</td>
</tr>
<tr>
<td>20</td>
<td>Varenicline tartrate</td>
<td>No (due 2020)</td>
</tr>
</tbody>
</table>

* Rank as per PHARMAC Annual Review December 2014 (1= highest, 20 = lowest).

Two of the items are inhalers used in asthma and other respiratory-related conditions (fluticasone with salmeterol and budesonide with eformoterol). A switch in NZ from originator to generic brands of a similar pharmaceutical, salbutamol, was met with opposition by doctors and patients in 2005, and, despite an NZ study demonstrating equivalence, three brands are now listed in the Schedule, with the originator brand partly funded (patients pay the excess cost). Resistance to brand changes for these other inhalers might be anticipated. Finally,
venlafaxine and risperidone both (still) consume a significant portion of the annual budget, with the (unlikely) possibly that this is due to increased consumption. More likely is the scenario that use of the funded originator brands of both risperidone injection and oral disintegrating tablet are responsible, and the low use of generic venlafaxine observed in this study. As generic versions for these medicines are available, opportunity exists for significant savings to be made.

The ‘top 20 by cost’ list is merely a glimpse into the preparations in the Schedule, and can serve to focus efforts where significant economic gains might be made. There are, however, more medicines in the overall Schedule which are currently funded as originator brands and which over time will be available as generics.

7.1.4. Health datasets can be used to evaluate pricing policies

One of the major facilitators in using the New Zealand health datasets is the unique patient identifier – the NHL. It is this identifier which enables the linking of the pharmacy dataset with hospital and other health services data. Prior to 2007, rates for completion of NHIs were low—estimates in the order of 72–88% completion have been reported on in other studies; however, completeness in the data used in the case studies in this thesis was of the order of 6% for lamotrigine (years 2004 to 2009) and less for the other medicines using more recent data.

One of the limitations noted in this thesis is the absence of data at primary care level. Visits made to a general practitioner are not centrally recorded, nor are interactions with other community-based services. To address this limitation, it may be necessary to conduct separate studies at PHO level where patient notes are housed.

Despite these limitations, the New Zealand health datasets can be used to evaluate the impact of reference-pricing, and provide evidence which can be used to guide further pricing policy-making. Accessing the datasets with near ‘real-time’ information technology could be a means to computerised monitoring of policies as they are implemented – a post-policy implementation system like that of post-marketing surveillance. A ‘flagging’ mechanism could be added to alert relevant agencies of the incidence of adverse health events or of deviation from the policy, similar to the Intensive Medicines Monitoring system previously conducted by the New Zealand Pharmacovigilance Centre at the University of Otago. Such a system, integrated into a series of well-conducted studies could produce more rapid, albeit still retrospective, outcomes and recommendations.
Further study

This thesis, however, limited itself to the issue of generic reference pricing. A natural next step might be to examine therapeutic reference pricing, such as the at ATC therapeutic group 3 or 4.\footnote{Example: Risperidone is in ATC therapeutic group 5, within ‘Other antipsychotics’ (TG 4), within ‘Antipsychotics’ (TG 3), within ‘Psycholeptics’ (TG 2), within ‘Nervous system’ (TG 1).} PHARMAC has in the past conducted therapeutic reference pricing for ACE inhibitors, calcium channel antagonists and the ‘statins’, and the debate on the superiority of one medicine over another in reference groups is still relevant. As new pharmaceutical medicines are brought to the market, unless they are truly innovative and first-in their therapeutic class, justification to enter a therapeutic class and be funded must be made. New entities on the horizon include anti-rheumatic medicines and medicines used in epilepsy and chronic obstructive pulmonary disease amongst others, (although these are yet to be proposed to PHARMAC for funding). Establishing grounds for therapeutic reference pricing by examining past experiences could assist PHARMAC, and similar agencies internationally, in future funding decisions. In addition, prospective examination of substitutions made with biosimilars would be informative in this emerging field of interchangeability of biogenetically derived medicines.

7.2. The way forward: Is it time for a generic medicines policy?

Despite the ability of PHARMAC to achieve considerable savings from using policies which regard most medicines equal irrespective of brand, points of weakness exist in the supply and management of pharmaceuticals, some of which have been highlighted in this thesis. In turn these deficiencies are open to exploitation and result in a waste of resources.

Reviews of studies suggest that concerted policies, or at least combinations of interventions, are more effective than single efforts to manage pharmaceutical expenditure. In this regard, PHARMAC is not, nor should the agency be, the only actor in encouraging the use of generic medicines, with this thesis highlighting the central role of the pharmacist. Furthermore, it is evident that adverse consequences of policies occur and that readjustment is sometimes needed, again highlighted in this thesis by the case of SA exemption policies and the simultaneous funding of multiple brands including the originator.

Other aspects of the NZ pharmaceutical system detract from a concerted voice on generic medicines. Information technology systems used in general practice are not oriented towards generic prescribing, nor to generic labelling in pharmacies, and there is no legislative requirement and no incentive in place for either. Self-audited direct-to-consumer advertising of prescription medicines is permitted in NZ, and is directed at promoting brand awareness and
modifying patient behaviour away from generic equivalents. In addition the pharmaceutical industry has strong alliances with patient-interest groups.

The science on bioequivalence of non-biological medicines is clear and clinical equivalence has been established in this thesis for four medicines addressing complex health conditions. The opportunity for financial advantage in preferentially using generic medicines is within easy reach, yet wholesale endorsement by the medical sector is lacking. If medical professionals are unconvinced, patients cannot be expected to be either. The advent of expensive and complex medicines together with increasing expectations from the pharmaceutical budget necessitates wisdom on generic and biosimilar medicines from all. A concerted policy, and the conversations and debate that such a policy would necessitate, might add efficiency to the pharmaceutical delivery system in NZ.

7.3. Conclusion

This thesis questioned the legitimacy of generic reference pricing in New Zealand in terms of the clinical consequences and patient understanding of the policy. Using a difference-in-differences analysis of data extracted from centralised health databases, no effect of brand switching on a ‘whole of population’ cohort for four selected medicines of relevance in mental health conditions could be found. Patients who switched brands because of generic reference pricing fared no worse than non-switchers.

The challenge for New Zealand, and countries internationally, to provide pharmaceutical therapy in a sustainable, equitable and efficient manner is set to persist as technology evolves and demands for supply escalate. The use of defined pricing policies, and monitoring their implementation and impact, such as conducted in this thesis, are critical in the management of pharmaceutical expenditure.
Appendix 1: Sample Questionnaire

Questionnaire: Medicine (brand) switches in New Zealand from the patients’ perspective

Information about the questionnaire
This questionnaire is anonymous. No information that is provided will be identifiable to you. If you do not wish to participate simply place your questionnaire in the return box/envelope. Your pharmacist will not know if you have completed the questionnaire or not.

Please note by completing the questionnaire you will be deemed to have given your consent to participate in this study. Please ask your pharmacist to explain this if you are unsure.

Section A:

1. Which brand of statin (medicine for cholesterol) are you currently taking? (Tick a box)
   - Lipitor
   - Zostar
   - Apo-atorvastatin
   - Dr Reddy’s Atorvastatin
   - Lontstat
   - Zocor
   - Lipex
   - Apo-simvastatin
   - Simio
   - Simvastatin-Pfizer
   - Simvastin
   - Arrow-Simva
   - I don’t know

2. How many times have you switched brands of statins? (Tick a box)
   - Never switched
   - Just the once
   - I don’t know
   - Switched more than once

3. If you never switched brands, please tell us why not? (Tick as many as apply)
   - I didn’t know I could switch
   - I heard bad things about the new medicine on the radio
   - I’ve had a bad experience with medicines in the past
   - It is my right to choose
   - I saw the TV adverts telling me I didn’t have to switch
   - I heard bad things about the new medicine from a friend/family member
   - I don’t want to risk my condition getting worse
   - I can afford to pay for the original one
   - Other: ______________________________

4. Have you ever changed back to the first brand; the brand you were taking before?
   - No
   - Yes

5a. If you stayed on the new medicine, why didn’t you switch back? (Tick as many as apply)
   - I had no problems with the new medicine
   - My pharmacist/doctor explained the change to my satisfaction
   - I didn’t know I had a choice
   - I can’t afford to pay for the alternative
   - Other: ______________________________

5b. If you switched back, why did you switch back to the original medicine? (Tick as many as apply)
   - My doctor told me to
   - The new one made me sick
   - The new one didn’t work properly/my condition got worse
   - A friend told me about switching
   - Other: ______________________________

ix Actual questionnaire delivered was modified to match the medicines listed in questions 1 and 2 to that which the patient was using and hence had been selected for.
6. On a scale of 1 to 6, where 1 = unnecessary and 6 = life-saving, how important do you consider this medicine (the statin) to your health? (Circle a number)

<table>
<thead>
<tr>
<th>Unnecessary (I don't think I need it)</th>
<th>Life-saving (I might die without it)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Section B:

I. If there have been any extra costs related to switching brands, please tell us how much it **has cost you**, (an estimate will do):

<table>
<thead>
<tr>
<th>APPROXIMATE COST ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel costs</td>
</tr>
<tr>
<td>Fees paid</td>
</tr>
<tr>
<td>Time off work</td>
</tr>
</tbody>
</table>

   a. Extra costs associated with the doctor
   b. Extra pharmacy costs
   c. Extra laboratory visits
   d. Other: (Please explain)

II. Thinking about switching between **medicines in general**, please tell us how you feel about each of the following: (mark the box):

<table>
<thead>
<tr>
<th>Strongly agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>If I choose a medicine different to the fully funded one, I must pay for it</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the new medicine doesn't suit me, I must be able to switch back with no extra charge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I should not have to switch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

III. Currently patients must pay $5 for each prescription item, with the government using taxes to pay for the balance. Please tell us how you feel about each of the following: (mark the box)

<table>
<thead>
<tr>
<th>Strongly agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>All medicines should be free of charge for everyone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certain medicines should be free of charge for everyone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines for certain people should be free of charge (for e.g. elderly, children, other)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People who can afford it, should pay the whole amount for their medicines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everyone should pay a percent of the cost of their medicines, and not just the $5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines should be paid for by private health insurance not taxes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IV. Where did you first hear about brand switches? (Tick a box)

- □ Pharmacist
- □ Nurse
- □ Other: ________________________
- □ Doctor
- □ TV/Radio
- □ Never heard about them

V. Please complete the following statement which best fits your belief about paying for choice. (Tick one box only)

"To be able to choose which brand of medicine I take, I am willing to pay......"
- □ $5 per month
- □ $10 per month
- □ $20 per month
- □ $35 per month
- □ $50 per month

There is no limit on how much I am willing to pay

Section C:

Finally, please complete the following information (mark/completion the box):

a. Are you?
- □ male, or □ female

b. In which year were you born?

19 ______

c. How many people live in your home? (Just a number in each box)

- □ older adults <65
- □ adults 16yr - 65yr
- □ children under 5
- □ children 5-15yrs

d. What is your highest level of education? (Tick a box)

- □ Primary school
- □ Trade qualification
- □ Secondary school
- □ University diploma/degree

e. To which ethnic group do you belong? (Tick a box)

- □ NZ European
- □ Maori
- □ Indian
- □ Korean
- □ Other European
- □ Other Pacific Island
- □ Chinese
- □ Other: ________________________

f. Thinking about this month, how many different medicines do you take each day? (Tick a box)

- □ 1
- □ 2
- □ 3
- □ 4
- □ 5
- □ 6
- □ more than 6
- □ none on a daily basis

[Please turn over]
g. Adding up all people earning in your household, what is the total income in your home (tick a box)?

<table>
<thead>
<tr>
<th>After tax weekly income $</th>
<th>After tax fortnightly income $</th>
<th>Before tax annual income $</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ up to 86</td>
<td>□ up to 172</td>
<td>1 - 5,000</td>
</tr>
<tr>
<td>□ 87 - 172</td>
<td>□ 173 - 343</td>
<td>5,001 - 10,000</td>
</tr>
<tr>
<td>□ 173 - 256</td>
<td>□ 344 - 512</td>
<td>10,001 - 15,000</td>
</tr>
<tr>
<td>□ 257 - 335</td>
<td>□ 513 - 671</td>
<td>15,001 - 20,000</td>
</tr>
<tr>
<td>□ 336 - 414</td>
<td>□ 672 - 829</td>
<td>20,001 - 25,000</td>
</tr>
<tr>
<td>□ 415 - 493</td>
<td>□ 830 - 987</td>
<td>25,001 - 30,000</td>
</tr>
<tr>
<td>□ 494 - 573</td>
<td>□ 988 - 1,145</td>
<td>30,001 - 35,000</td>
</tr>
<tr>
<td>□ 574 - 652</td>
<td>□ 1,146 - 1,303</td>
<td>35,001 - 40,000</td>
</tr>
<tr>
<td>□ 653 - 805</td>
<td>□ 1,304 - 1,610</td>
<td>40,001 - 50,000</td>
</tr>
<tr>
<td>□ 806 - 939</td>
<td>□ 1,611 - 1,879</td>
<td>50,001 - 60,000</td>
</tr>
<tr>
<td>□ 940 - 1,074</td>
<td>□ 1,880 - 2,147</td>
<td>60,001 - 70,000</td>
</tr>
<tr>
<td>□ 1,075 - 1,459</td>
<td>□ 2,148 - 2,918</td>
<td>70,001 - 100,000</td>
</tr>
<tr>
<td>□ 1,460 - 2,102</td>
<td>□ 2,919 - 4,203</td>
<td>100,001 - 150,000</td>
</tr>
<tr>
<td>□ 2,103+</td>
<td>□ 4,204+</td>
<td>150,001+</td>
</tr>
</tbody>
</table>

h. Have you or any member of your family experienced an adverse reaction (unexpected and unwanted reaction) to a medicine? (Tick a box)

- □ No
- □ Yes, me
- □ Yes, a family member

Thank you for completing this questionnaire! Please fold it and place it in the box at the pharmacy.

This study has been approved by the University of Auckland Human Ethics Committee on 19 April 2013; Reference number 9254, for 3 years.
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