THE IMPACT OF THE INTRODUCTION OF GENERICS AND GENERIC REFERENCE PRICING ON CANDESARTAN AND ROSUVASTATIN UTILISATION, PRICE AND EXPENDITURE IN SOUTH AFRICA

By (Mr) Henk de Jager

214571769

Submitted in partial fullfillment of the requirements for the degree of M. Pharm (M-PHPE) in the Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal.

Supervisor: Prof. Fatima Suleman

2017

DECLARATION

In fullfillment of the requirements of the coursework degree of Masters in Pharmacy in the Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa, I, Henk de Jager, declare as follows:

i. That the work described in this thesis has not been submitted to UKZN or other tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party.
ii. The research reported in this dissertation, except where referenced, is my original work.
iii. This dissertation does not contain other person's text, tables, data, graphs or other information, unless specifically acknowledged as being sourced from other persons.
iv. This dissertation does not contain other person's writing, unless specifically acknowledged as being sourced from other researchers. Where other written resources have been quoted, then:-
    a) Their words have been rewritten but the general information attributed to them has been referenced;
    b) Where their exact words have been used, their witing has been placed inside quotation marks, and referenced.
v. Where I have reproduced a publication of which I am the author, co-author, or editor, I have indicated in detail which part of the publication was actually written by myself alone, and have fully referenced such publications.

Signed: _____ Date: **09/11/2017**

ACKNOWLEDGEMENTS

Firstly, I would like to thank our Heavenly Father for the privilege of having the opportunity to further my academic career.

This thesis would not have been possible without the support of my fantastic wife, Yvonne. Thank you for your continued support throughout this whole endeavour. It wasn't always easy and it didn't always go according to plan, yet you stuck with me and I never felt alone. I will forever love you. To my big boy, Dian, daddy is so proud of you, and without even knowing it, you gave me the strength to carry on when things got tough. I also owe a big debt of gratitude to my parents for helping us with babysitting duties.

The management and directors of Mediscor PBM, thank you for your support and providing access to the data used in this study.

Lastly, I would like to thank my supervisor, Prof. Fatima Suleman, for helping with the conceptualization of the idea for this study, your continued support, understanding, and words of wisdom at just the right time to keep me on the right track and moving forward.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Description/Meaning
AED	Anti-epileptic Drug
EMA	European Medicines Agency
FDA	Food and Drug Administration
INN	International Non-proprietary Name
INR	International Normalised Ratio
MCC	Medicines Control Council
NDP	National Drug Policy
NTI	Narrow Therapeutic Index
PBM	Pharmacy Benefit Manager
PPI	Proton Pump Inhibitor
RCT	Randomised Controlled Trial
SEP	Single Exit Price
WHO	World Health Organization

LIST OF FIGURES AND TABLES

List of figures

List of tables

ABSTRACT

Rationale for the study

The growth of pharmaceutical expenditure as a percentage of total health care expenditure has stagnated, both locally and globally, despite increasing consumption. Two factors that contributed to the stagnation are the introduction of generic medicines after patent expiry, and the introduction of cost-containment policies, like generic reference pricing. The introduction of generic medicines offer the opportunity to reduce medicine expenditure because of a switch in utilisation from expensive brand-name originator products to more cost-effective generic alternatives. Reference pricing is a policy where therapeutically similar medicines are grouped together, and a maximum reimbursement rate is set for the group. If a patient chooses to use a product more expensive than the reference price, they have to pay the difference in price. In the South African context, generically similar products are grouped together and the reimbursement rate is set at the average price of the generically equivalent products.

Aims and objectives

The aim of the study is to determine the impact of the introduction of generics and generic reference pricing on two active ingredients, candesartan and rosuvastatin, which recently lost their patent protection, in the South African private health care sector, for the period January 2012 to December 2015. To achieve this aim, three objectives were identified:

1. To measure the impact on medicine utilisation after the introduction of generics and generic reference pricing on candesartan and rosuvastatin.
2. To measure the impact on the average medicine price after the introduction of generics and generic reference pricing on candesartan and rosuvastatin.
3. To measure the impact on medicine expenditure after the introduction of generics and generic reference pricing on candesartan and rosuvastatin.

Method

Medicine claims for candesartan and rosuvastatin was obtained from a Pharmacy Benefit Manager in South Africa. The claims covered a 48-month period from January 2012 to December 2015 and provided a pre- and post-reference price period for analysis. Medicine

utilisation was measured as the number of Defined Daily Doses dispensed per 100 000 beneficiaries. Medicine price and expenditure was calculated as the average per Defined Daily Dose.

Results

Candesartan experienced an average 7.0% year-on-year decline in utilisation and rosuvastatin a 5.0% increase. Utilisation of generic medicines was 59.3% of the total volume in the final year of the study for candesartan and 76.4% for rosuvastatin. The introduction of generic alternatives resulted in a 31.0% reduction in the average price per Defined Daily Dose for candesartan and a 13.9% reduction for rosuvastatin. Medicine expenditure reduced by an additional 34.6% and 20.9% for candesartan and rosuvastatin respectively, because of the introduction of generic reference pricing. The total saving because of the introduction of generics and generic reference pricing was 54.8% for candesartan and 31.9% for rosuvastatin.

Conclusion

The introduction of generics and generic reference pricing did not have an impact on overall medicine utilisation, but reduced the price and expenditure of both candesartan and rosuvastatin.

CHAPTER 1

1. INTRODUCTION

Pharmaceutical expenditure is still increasing internationally, although growth has slowed down since the mid-2000's [1, 2]. According to a recent Organisation for Economic Co-operation and Development (OECD) report, Health at a glance 2015, pharmaceutical expenditure has reached $80 billion in OECD countries in 2013 [1]. QuintilesIMS predicts that worldwide pharmaceutical sales will be 30% higher in 2018 than it was in 2013 [2]. This growth will mostly be because of growth in the United States (US) market and in developing countries, like South Africa, while growth in the top 5 countries in the European market (Germany, United Kingdom (UK), France, Italy and Spain) is predicted to be between one and four percent in the same period [2]. In South Africa, pharmaceutical expenditure in the private sector reached ZAR 22.3 billion in 2015, a 36.8% increase from the ZAR 16.3 billion spent in 2012 [3].

The introduction of new medicines and the increasing demand for existing medicines are the main drivers of pharmaceutical spending. The quantity of medicines consumed has increased over time in many therapeutic classes. Most notably, between 2000 and 2013, the use of antihypertensive medication in OECD countries nearly doubled, while the use of cholesterol lowering drugs tripled [1]. In South Africa, a similar trend of increasing consumption can be seen, with hypertension prevalence increasing from 114.6 per 1 000 beneficiaries in 2011 to 152.8 per 1 000 beneficiaries in 2015 [3].

Despite the nominal growth in pharmaceutical expenditure and the increased consumption, pharmaceutical expenditure as a percentage of total health expenditure has reached a plateau [1, 2]. Pharmaceutical expenditure was responsible for between 17% and 20% of total health expenditure in OECD countries in 2013 [1]. The 3.2% drop in pharmaceutical expenditure in the five year period since 2009 is in sharp contrast to the average 2.7% growth each year in the preceding five years. Prior to 2005 spending on retail pharmaceuticals grew at a faster rate than other health care sectors and was a major contributor in driving overall health care expenditure [1]. In South Africa, pharmaceutical expenditure contributed 16.1% to overall health expenditure in the private sector in 2015, only marginally more than the 15.8% in 2012 [3].

Two factors that contributed to the stagnation in growth of pharmaceutical expenditure is the introduction of generic medicines and the introduction and strengthening of cost-containment policies [1, 4]. According to the World Health Organization (WHO), a generic medicine is defined as "a pharmaceutical product, usually intended to be interchangeable with an innovator product, that is manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusive rights" [5]. Generic medicines offer the opportunity to make substantial savings without affecting the quality of care [6]. In the US market, the price of generic medicines are 80% to 85% lower than the brand name product [1]. The introduction of generic medicines sees dramatically lower volume utilisation of the more expensive brand name products, which results in savings in pharmaceutical expenditure [2]. In the top 5 markets in Europe the introduction of generic medicines has had an impact of more than $16 billion every year since 2006 [2]. In South Africa, generic medicines are 22 % cheaper than their brand name equivalents, and 56% cheaper than products without any generic competition [5]. Generic medicines were responsible for 56.2% of all medicines dispensed in South Africa in 2015 [5].

Although the introduction of generic medicines played an important role in containing medicine expenditure in the last decade, there are other cost containment strategies used world-wide that also contributed to the stagnation in growth [4]. One of the cost-containment policies used to promote the use of generic medicines is reference pricing. In essence, reference pricing groups therapeutically similar medicines together and sets a maximum reimbursement rate for the group of medicines [7]. Any medication with a price below the reference price will be covered, i.e paid, in full, while medicine with a higher price will only be partially reimbursed with the beneficiary paying the balance between the price of the chosen medicine and the reference price. Reference pricing is not a price control. It has an indirect impact on medicine expenditure through medicine use changes [7]. Reference pricing can change the demand for expensive brand name medicines, when people elect to use cheaper generic alternatives to avoid out-of-pocket co-payments. Three levels of reference pricing exist [7]. In level one, medicines that have identical bioactive ingredients and are considered therapeutically interchangeable, are grouped together. This is also referred to as generic reference pricing. This type of reference pricing has been implemented in Canada (Ontario), Denmark, Italy, Norway, Sweden and the USA [7]. Level two reference pricing groups medicines in analogue groups. The medicines are chemically slightly different, but have comparable or identical indications. This is also referred

to as therapeutic reference pricing. Therapeutic reference pricing has been implemented in British Columbia, Canada [7]. In level three, all medicines used to treat a condition are grouped together. Examples where level three reference pricing has been implemented include Netherlands and Germany [7]. Reference pricing at level one has less risk of adverse effects, however the potential for savings is also less at level one [7]. In South Africa the first applications of generic reference pricing (level one reference pricing) can be found as far back as 2005 [8]. Reference pricing does not have adverse effects on health outcomes [7, 9]. It also did not increase the use of other health services, with the possible exception of an increase in doctors consultations when reference pricing is introduced and patients want to switch to cheaper reference medicines [10].

There are numerous studies analysing the impact of generic medicines on pharmaceutical expenditure, as well as the impact of generic reference pricing on pharmaceutical expenditure. Data from low and middle income countries, like South Africa, however remain limited. The aim of this study was to determine the impact of the introduction of generics and generic reference pricing on candesartan and rosuvastatin, utilisation, pricing and expenditure for the period January 2012 to December 2015, in an environment where generic reference pricing was already applied on other unprotected pharmaceutical products. The impact was measured on medicine utilisation, the average medicine price as well as the impact on medicine expenditure. This study will help answer the question whether reference pricing has longer term benefits after the initial introduction of the reference pricing policy, which usually results in a reduction in medicine expenditure.

To answer the research question, medicine claims for candesartan and rosuvastatin from a Pharmacy Benefit Manager (PBM) in South Africa was analysed using a retrospective longitudinal research design. A longitudinal study is one that takes place over time, with two or more waves of measurement [11]. A longitudinal database of all the claims that met the inclusion criteria was constructed. A longitudinal database is a searchable mass of computerised data providing information about individuals over time [12]. A list of all the fields and descriptions of the database can be found in Appendix 1. The database includes demographic information about the beneficiaries, including date of birth, age and gender. For confidentiality, all beneficiary identification numbers were decoded and de-identified. Authorisation was obtained from the PBM to use the claims data for the study (Appendix 2). To ensure the reliability and validity of the results, a list of quality criteria suggested by Ramsay et al. (1980)

was adopted when the research methods and tools were designed [13]. The list of the quality criteria and their application can be found in Appendix 3.

CHAPTER 2

2. LITERATURE REVIEW

2.1 Generic medicine

2.1.1 Definition and application

There are many definitions used for generic medicines around the world. The WHO defines generic medicine as:

> *" a pharmaceutical product which: is usually intended to be interchangeable with an innovator product, is manufactured without a licence from the innovator company, and is marketed after the expiry of the patent or other exclusive rights"* [5].

The US Food and Drug Administration (FDA) defines generic medicine as:

> "*a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use*" [14].

Finally**,** the European Medicines Agency (EMA), which oversees EU-wide authorisation of medicines, defines a generic medicine as:

> "*a medicine that is developed to be the same as a medicine that has already been authorised (the 'reference medicine'). A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s) as the reference medicine. However, the name of the medicine, its appearance (such as colour or shape) and its packaging can be different from those of the reference medicine*" [14].

Despite the numerous definitions used world-wide, generic medicines are generally understood to be medicines not protected by a patent, which is bioequivalent to a medicinal product already authorised, with the same qualitative and quantitative composition of active ingredients, the same pharmaceutical form, and the same therapeutic indications [15]. If these conditions are

met, generics are considered to have an equivalent clinical effect when substituted for the original brand-name product [16].

One of the main principals used to ensure comparable safety and efficacy between original products and their generic equivalents, is bioequivalence [14]. Bioequivalence has been defined as follows:

> "*two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects , with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration, and meeting the same or comparable standards*" [14].

The bioequivalence standards for generic medicines used internationally is very similar. Both the US FDA and the EMA require that generic medicines demonstrate a bioavailability of 0.80 - 1.25 compared to the originator drug [14, 17]. There are however differences between countries for the standards of Narrow Therapeutic Index (NTI) medicines. In the US the same standard of 0.80 - 1.25 is used for NTI medicines, while in Europe the bioavailability for NTI medicines has a tightened acceptance level of 0.90 - 1.11 [14]. In Australia there are no generic versions of digoxin or phenytoin, and the two brands of warfarin available in the Australian market are not considered interchangeable [14]. In South Africa, the Medicines Control Council (MCC) also use the 0.80 - 1.25 bioavailability standard, but provision is made to use a non-South African product as the reference standard [17]. A study of 135 generic products available in South Africa, could not find any differences between originator brands, branded generics or unbranded generics [18]. The tolerance levels allowed for bioavailability for generic medicines have been favourably compared to those acceptable for inter-batch variation during production of the originator medicine [14]. Because of the bioequivalence standards, most countries world-wide allow an abbreviated registration process for generic medicines, where pre-clinical and clinical studies do not have to be performed by the generic medicine manufacturer [14].

Generic substitution is a policy that allow the dispenser of medicine to substitute a brand-name product with a cheaper generic alternative [16]. Depending on the jurisdiction, this substitution

can be performed with or without consulting the prescriber of the medicine [19]. Implementation of a generic substitution policy has been found to stimulate generic use and reduce pharmaceutical expenditure [19].

2.1.2 Safety and efficacy

The major argument opponents of generic medicines and generic substitution has, is the issue surrounding the safety and efficacy of generic medicines. Specifically, how does the safety and efficacy of generic medicines compare to their originator counterparts. Several studies have been published on the subject. Kesselheim et al. (2008) published an extensive systematic review and meta-analysis on the clinical equivalence between generic and brand-name medicines used in the treatment of cardiovascular disease [20]. The 47 studies in their sample included 8 subclasses of cardiovascular medicines, including two types of NTI medicines. The clinical outcomes that were measured included: clinical laboratory values such as International Normalised Ratio (INR) and urine electrolytes; adverse effects or other morbidity; and health care system utilization, including clinic and emergency department visits. They concluded that generic and brand-name cardiovascular medicines are similar in nearly all clinical outcomes [20]. Data extrapolated from two large randomised controlled trials (RCTs) published in the early 2000's, Controlled-ONset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) and Antihypertensive and Lipid-Lowering treatment to Prevent Heart Attack (ALLTHAT), also found that there was no difference in clinical outcomes between brand-name originator medicines and their generic equivalents, but that other factors such as race and adherence to therapy are more likely to influence clinical outcomes [21].

While the active pharmaceutical ingredient is the same in originator brand-name products and their generic equivalents, there might be a difference in excipients used in the products. A number of excipients are known to have side-effects or contra-indications [14]. Gothe (2015), also argues that decreased quality of excipients and manufacturing quality can impact the release and intended action of the active ingredient in generic medicines, but found no difference in clinical outcomes between originator medicines and their generic counterparts [16].

There are, however, still some controversy regarding generic substitution in specific therapeutic medicine categories, specifically anti-epileptic drugs (AEDs). Significant problems have been reported, including breakthrough seizures and increased side effects following a switch to a generic AED [14]. Dunne (2013) concluded that, at least in the case of AEDs, bioequivalence, as defined in regulations, does not always correspond to therapeutic equivalence because of the permitted range, evaluation methods and individual variation [14]. A systematic review and meta-analysis on seizure outcomes following generic substitution by Kesselheim et al. (2010), refutes this claim and found that the available evidence does not suggest an association between loss of seizure control and generic substitution in at least three types of AEDs [22].

2.1.3 Medicine utilisation

Utilisation of generic medicines has been increasing in Europe and the US in the last decade [1, 2]. In Europe, generic medicines were responsible for almost half of the volume of medicines dispensed in 2009 [23]. In 2013, this number increased to almost 76% [1]. There is, however, significant variations in generic utilisation between countries in Europe. European countries with higher generic utilisation rates included the UK and Germany (65% of volume in 2009) [24, 23], and the Netherlands (more than 50% of volume in 2007) [19]. European countries at the lower end of the generic utilisation spectrum include France (40% of volume) [23], Spain (30% of volume) [23] and Italy (28% of expenditure) [15]. In the US, generic medicines represent about 70% to 80% of the total medicine volume [23, 25]. Data for countries outside Europe and the US is much more limited. Latin American countries have a generic utilisation rate comparable with the US and Europe [23], while in China generic medicines only represent approximately 34% of the total volume of medicines dispensed [26]. In South Africa, in 2015, generic medicines were responsible for 56% of the volume of medicines dispensed, and 41% of medicine expenditure [5].

Market structures (including number of off-patent medicines) and prescribing practices are responsible for some of the differences in generic uptake between the countries, but generic utilisation can also be stimulated through pharmaceutical policies [1]. In the Netherlands, for example, the potential cost savings because of the use of generic medicines was recognised early, and policies such as generic substitution was implemented and expanded to stimulate growth [19]. Apart from generic substitution, countries can also make use of International Non-proprietary Name (INN) prescribing practices, financial incentives to physicians and

pharmacists, reduced co-payments for (or zero co-payments) on generic medicines, and reference pricing to stimulate growth in the generic medicines market [1].

2.1.4 Medicine Price

In most jurisdictions around the world, generic medicines qualify for an abbreviated application process where no pre-clinical and clinical studies are required, but bioequivalence to the originator medicine must be demonstrated. The abbreviated registration process is one of the main reasons for the price difference between generic and originator medicines [14].

The magnitude of the variation in price between generics and originator medicine differs between countries around the world. Just in Europe, the difference is generally between 20% to 80%, depending on the country [26]. In Spain there is almost no difference between the price of the generic medicine and their originator product [27], in Italy it is between 40% and 60% [15], and up to 90% for some products in the UK and the Netherlands [27]. In South Africa, in a sample of 346 medicines used in the treatment of cardiovascular disease, 75% of the generic medicines were more than 40% cheaper than their branded version [28].

Generic competition, in general, changes the market and decreases the price of medicines [26]. Some countries are however more successful in managing to reduce the price of generic medicines. This can be achieved through local price regulations, reimbursement arrangements, demand-side pressures (e.g. education), and reference pricing [14].

2.1.5 Medicine expenditure

Due to their lower price and comparable safety and efficacy, an increase in generic medicine utilisation will result in a decrease in medicine expenditure [26]. In the US, in 2010 alone, the use of generic medicines saved the American health system US$158 billion, or an average of US$3 billion every week [14]. A study by Sheingold (2014), found that the shift toward less expensive generic medicines had cut in half the rate of increase in the price of a prescription on Medicare Part D in the US. A further saving of 60% of total Part D spending was possible if a

100% generic dispensing rate for eligible products was achieved [25]. Zeng (2013), found a saving of more than 60% in costs because of generic substitutions in China [26].

An unintended consequence of generic substitution is an increase in adherence. This could be due to reduced out-of-pocket expenses for patients, which have been associated with increased medication adherence [21, 15, 29]. The increase in adherence could lead to savings in other health care segments, e.g. preventing avoidable hospitalisations [21].

Although switching from originator medicines to their generic counterparts could save money in principle, in practice it is often more complex and dependant on a host of other factors [23]. Gothe (2015), argues that because of a higher rate of adverse events associated with generic substitution in certain therapeutic groups, overall health care expenses may exceed the amount saved by the lower acquisition costs of generic medicines [16]. It must however be noted that the study focussed only on sensitive therapeutic categories which included NTI medicines, and was in part funded by a manufacturer of originator medication. There are however, other ways to increase generic utilisation, as outlined in the next section.

2.2 Reference pricing

2.2.1 Definition and application

The term reference pricing might be confusing in the economic sense, because the name implies that it is a pricing policy, whereas in reality, reference pricing is a reimbursement policy [30]. Under reference pricing, medicines that are deemed to be therapeutically equivalent or interchangeable are grouped together (referred to as a reference group), and a maximum reimbursement rate is set for the group of medicines [14, 31]. The reimbursement rate for a specific group can be the price of the lowest cost product in the reference group, or it can be based on an average price of all the products in the group [31]. If a medicine at a higher price does not buy greater effectiveness or reduced toxicity, then 3rd party insurers in resource constrained settings should not cover the extra costs [30]. If a patient elects to use a product more expensive than the reference price, they will pay the difference in price between the elected product and the reference price [14, 32]. Reference pricing has widespread international application, beginning in Germany in 1989, followed by the Netherlands and New Zealand shortly thereafter, and more than a dozen countries since [33].

According to Aaserud (2007) reference pricing can be applied to different levels of reference groups. In level one, medicines that have identical bioactive ingredients and are considered therapeutically interchangeable are grouped together. This is also referred to as generic reference pricing. This type of reference pricing has been implemented in Canada (Ontario), Denmark, Italy, Norway, Sweden and the USA [7]. Level two reference pricing groups medicines in analogue groups. The medicines are chemically slightly different, but have comparable or identical indications. This is also referred to as therapeutic reference pricing. Therapeutic reference pricing has been implemented in British Columbia, Canada [7]. In level three, all medicines used to treat a condition are grouped together. Examples where level three reference pricing has been implemented include Netherlands and Germany [7]. Reference pricing at level 1 has less risk of causing adverse effects, but the potential for savings is also much less because the reference group is restricted to brand and generic versions of the same active ingredient [7].

Reference pricing is not a price control, because retail prices are not set. It is rather an indirect method of price control or a reimbursement pricing system [7]. Manufacturers are free to set a price above the reference price, but then the patient has to pay the difference in price. Reference pricing has also been called incentive pricing because it provides incentives to direct prescribing and providing in favour of less expensive reference medicines [30]. It is designed in such a way that financial incentive and initiative are shifted from the provider to the patient, which exposes the patient to the financial consequences of their medicine use [32].

2.2.2 Medicine utilisation

In general, the introduction of reference pricing causes a shift in utilisation away from more expensive cost share medicines, to cheaper reference medicines, without negatively affecting overall utilisation of the reference group [7, 33]. A systematic review by Aaserud et al. (2007), found that the use of reference medicines increased by 60% to 196% immediately after the introduction of the reference price policy, while the use of cost share drugs decreased by 19% to 42% [7]. The relatively higher increase in the use of reference medicines compared to the decrease in cost share medicines, indicates that the utilisation of reference medicines was at a much lower base than cost share medicine, before the implementation of the reference price policy. Schneeweiss et al. (2007) also found a switch away from cost share medicines towards reference medicines after reference pricing was introduced in British Columbia, Canada. The results were less dramatic, but still substantial, with a 10% to 50% switching rate to reference medicines [30].

The shift from cost share medicines to reference medicines could however, be price sensitive [34]. If the incentive for the patient to move to a reference medicine is weak because the price difference between the cost share medicine and the reference price is low, the patient is more likely to stay on the cost share medicine and pay the difference out-of-pocket [30]. The introduction of generic reference pricing in Australia illustrated the effect of the price difference on the switching rate between cost share and reference medicines. Fluoxetine had a large price difference between the originator medicine and the reference price, whereas ranitidine had a much smaller difference. After 12 months, the reference fluoxetine products had a greater utilisation rate than the originator product, while for ranitidine the reference products only reached 30% of the utilisation rate of the originator cost share product [34]. In British Columbia, Canada, the use of reference H2-antagonists increased by 379% after the introduction

of therapeutic reference pricing in 1995[35]. It must be noted that the introduction of reference pricing coincided with a policy to restrict access to proton pump inhibitors (PPIs) to patients who met certain eligibility criteria, which could skew the effect of the reference pricing policy on generic utilisation.

Similar to the generic substitution policy, reference pricing has also been associated with an increase in medication adherence [33]. McManus et al. (2001), however, found that the introduction of reference pricing without a policy of mandatory generic substitution had little effect on changing utilisation behaviour [34].

2.2.3 Medicine price

Reference pricing causes a decline in the price of medicines in the reference group [7]. A systematic review by Lee at al. (2012) found that 4 of the 9 reference pricing policies they identified resulted in a reduction of medicine prices of the reference group, with a mean reduction of 11.5% (range 7% - 24%) [33].

The magnitude of the price reduction is, however, very variable and depends on the level of reference pricing, the therapeutic class of the reference group as well as the jurisdiction in which the reference price policy is applied [7, 36]. The introduction of generic reference pricing in Sweden in 1993 resulted in an initial decrease in prices for medicines, with an average 19% reduction in price for medicines in the reference group [37]. The introduction of generic reference pricing by a large medical scheme administrator in South Africa in the early 2000's, showed that 66% of the products in the reference group experienced a price decrease in the first 12 months after the policy was introduced [38]. Although the prices of medicines in the reference group declined after the introduction of reference pricing in Germany and the Netherlands, prices for products not covered by the reference pricing policy have been reported to increase [37].

In general, reference pricing is effective in forcing prices down to the reference price, but manufacturers have a clear disincentive to lower prices below the reference price [31, 30]. Pavcnik (2005) reported that the originator brand-name products reduce their prices

significantly more than their generic counterparts [39]. Prices of generic medicines reduced on average by only 11% after the introduction of reference pricing in Germany, whereas the prices of branded products decreased on average by 26%. The lower reduction in generic prices is likely due to the disincentive to reduce the price below the reference price.

2.2.4 Medicine expenditure

Reference pricing can reduce medicine expenditure significantly for third party insurers [7]. The changes in expenditure can be composed of: a) a shift in utilisation from expensive cost share medicines to cheaper reference medicines; b) beneficiaries paying a larger part of the expenditure; and c) reduced prices.

Similar to the reduction in price, the reduction in third party expenditure also varies by therapeutic class [40, 35, 30]. Savings are largest when the highest priced product in the reference group is also the most utilised, and when the reference price is determined per unit dispensed and not per day of treatment [30]. The level of reference price applied also has an impact on the savings that can be achieved. Grootendorst et al. (2005) reported that reference pricing at level 1 (generic reference pricing) produced only one quarter of the savings of reference pricing at level 2 (therapeutic reference pricing) [36].

Depending on the benefit design, reference pricing can also lead to decreased co-payments for beneficiaries if there is no co-payment charged on reference medicines below the reference price [33].

2.2.5 Health and health care utilisation

Since reference pricing policies might affect medicine utilisation, they could also have an effect on health and other non-pharmaceutical health care utilisation [7]. However, no adverse effects on health have been associated with a reference pricing policy [30]. With regards to health care utilisation, three studies reported a slight increase of between 7% - 11%, in physician visits shortly after the introduction of the reference pricing policy [40, 7, 33]. The increase in

physician visits was most likely due to patients visiting their doctors to change from a cost share to a reference medicine.

2.3 Background to the South African pharmaceutical environment

South Africa is an upper middle income country and like most low and middle income countries there is pressure on resources because of growing demand, especially for health care services [41]. South Africa has a two-tiered health system with 8.8 million people (16% of the population), insured by private insurers, while the remainder of the country is dependent on the public health system [3, 42]. This study only focused on a subset of the 8.8 million people covered by private insurance.

After the first democratic election in 1994 a national drug policy (NDP) was developed in 1996 to "develop a pricing plan for drugs used in South Africa in the public and private sectors" [43]. Several legislative changes were required to South Africa's medicines law, the Medicines and Related Substances Control Act (Act 101 of 1965), to implement the changes proposed in the NDP [44]. Some of these changes included banning "sampling" and "bonusing" of medicines and the establishment of a pricing committee [45]. The aim of these changes were to create a transparent pricing system which would include a single exit price (SEP) for medicines. The SEP legislation which came into effect in 2003, created a single price at which pharmacists and other authorised health care professionals were allowed to sell medicines to the public in the private health care market. The SEP was initially defined as the weighted average of the medicine price in 2003 and thereafter an annual maximum price increase was published by the minister of health [45]. In addition to the SEP imposed on manufacturers, legislation was also introduced in 2004 to cap the professional fee pharmacies were allowed to charge for the dispensing of medicines [45]. Mandatory offer of generic substitution also became legal in 2003, which allowed pharmacists to substitute brand name products with a generic equivalent, without requiring approval from the prescriber of the medicine [45]. The legalisation of generic substitution paved the way for the introduction of generic reference pricing in the private health care sector in South Africa. The first applications of generic reference pricing in the South African health care market can be found as far back as 2005 [8, 38]. There is very little research

as to the impact of these policies on medicine use, price and expenditure in South Africa, and this study will hope to fill the existing evidence gap.

2.4 Pharmacology

2.4.1 Candesartan

Candesartan is an antihypertensive medicine which belongs to the therapeutic class of angiotensin II receptor blocking agents (ARB) [46]. The ARBs are a relatively new class of antihypertensive agents [47]. Unlike angiotensin converting enzyme (ACE) inhibitors, the ARBs has no effect on bradykinin metabolism and are therefore more selective blockers of angiotensin effects [46]. ARBs available in South Africa include candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan [48].

Mechanism of action

Angiotensin II causes direct vasoconstriction as well as stimulating the release of aldosterone, which causes the reabsorption of both water and sodium, resulting in an elevation of blood pressure [47]. Unlike ACE inhibitors, the ARBs do not affect the renin-angiotensin system [47]. Candesartan inhibits the effect of angiotensin II on its receptor, angiotensin type 1 (AT_1), thereby directly blocking angiotensin II-induced arteriolar vasoconstriction [46] [48]. This mechanism of action offers a more complete angiotensin II inhibition by interacting selectively with the receptor site [48].

Pharmacokinetic profile

Candesartan cilexitil is an ester prodrug that is converted to candesartan during absorption from the gastrointestinal tract [48]. Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolosis to the active ingredient candesartan. It is mainly excreted unchanged in the urine (33%) and faeces (67%). Absolute bioavailability is estimated to be 15% and half-life elimination is approximately 9 hours [47].

Indications

Candesartan is used for the treatment of essential hypertension, especially where left ventricular hypertrophy is present [48]. In cardiac failure, candesartan can be used in combination with ACE inhibitors, or as an alternative to ACE inhibitors [48]. ARBs are also used in the treatment of myocardial infarction and diabetic nephropathy [47].

Dosage

The adult dose for hypertension is 8mg once daily, which may be increased after 4 weeks to a maximum of 32mg once daily. The usual maintenance dose is 8-16mg once daily. For cardiac failure the initial dose is 4mg once daily, and can be increased at intervals of at least 2 weeks to a maximum of 32mg once daily [48].

Safety

Candesartan should be used with caution in pregnancy and in patients who previously experienced angio-oedema with an ACE inhibitor [48].

The side effects of ARBs are similar to those of the ACE inhibitors, with the exception of cough and angio-oedema, which are possibly mediated by bradykinin [46]. Common adverse effects include headache, dizziness, syncope, muscle weakness, hypotension, rash, inflammation, urticaria, pruritus, alopecia, dry skin, diarrhoea, abdominal pain, nausea, constipation, dry mouth, dental pain, and sinus disorders [47]. Common drug interactions include non-steroidal anti-inflammatory drugs (NSAIDs) (cause an increase in blood pressure and swelling), potassium supplements (increased potassium levels in the blood) and lithium [47].

2.4.2 Rosuvastatin

Rosuvastatin is a competitive inhibitor of HMG-CoA(3-hydroxy-3-methylglutaryl-coenzyme A) reductase. This therapeutic class of medicines is also known as statins or reductase inhibitors [46] [48]. These compounds are structural analogues of HMG-CoA [46]. The main therapeutic

effect of statins is the reduction of artherogenic lipoprotein levels as a result of the inhibition of HMG-CoA in the liver. The reductin of artherogenic lipoproteins also have other benefits including enhanced stability of atherosclerotic lesions, and improved function of vascular endothelial cells [49]. Statins available in South Africa include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin [48].

Mechanism of action

HMG-CoA reductase mediates the first committed step in sterol biosynthesis. Statins induce an increase in low-density lipoprotein (LDL) receptors, which causes an increase in the fractional catabolic rate of LDL in the liver, as well as an increase in the liver's extraction of LDL precursors. This results in a reduction in the plasma pool of LDL [46]. At maximal doses, the reduction of LDL cholesterol can be up to 60%. Variable increases in HDL and modest decreases in triglyceride levels have also been noted after treatment with statins [46] [48].

Pharmacokinetic profile

Rosuvastatin has a high first pass extraction by the liver, but this is not entirely undesirable because the liver is the primary site of action of the statins [48]. The dose response curve for rosuvastatin is approximately linear [49]. Most of the absorbed dose is excreted in the bile and about 5-20% is excreted in the urine [46]. Rosuvastatin has poor bioavailability (20%) due to its extensive first-pass metabolism. Elimination half-life is approximately 19 hours, about 10% is metabolised and 90% eliminated unchanged in the faeces [48]. Food intake decreases the rate of absorption of rosuvastatin, but not the extent of absorption [50].

Indications

HMG-CoA inhibitors can be used alone or in combination with bile acid-binding resins in the treatment of severe hypercholesterolaemia, hign-risk moderate hypercholsterolaemia, and may also be effective in some cases of mixed hyperlipidaemia [48].

Dosage

To obtain a 25-30% reduction in LDL cholesterol, approximately 2.5mg of rosuvastatin is required. A doubling of the dose will provide another 6% reduction. Initially, an oral dosage of 5mg once daily, adjusted after 2 weeks if necessary with a range of 10-40mg once daily [48]. Most of the synthesis of cholesterol occurs at night, and therefore the shorter acting statins should also be given at night. Since Rosuvastatin is a longer acting statin, it can be taken at any time [48].

Safety

Rosuvastatin is contraindicated in hepatic disease or in patients with elevated serum transaminases [48]. Rosuvastatin should be used with caution in women who are pregnant or who are likely to become pregnant. Use in children is restricted to those with heterozygous familial hypercholesterolaemia [46].

Common adverse effects include abdominal pain, constipation, diarrhoea and flatulence, nausea, dyspepsia, headache, insomnia, sleep disturbances, skin rash, peripheral neuropathy, memory loss, sexual dusfunction, depression, angio-oedema, hypotension and interstitial lung disease. Rhabdomyolysis with renal failure has occured and the incidence and severity of myopathy are increased by drug interactions. Common drug interactions include ciclosporin, fluconazole, itraconazole, gemfibrozil, lopinavir, ritonavir (all cause increased rosuvastatin levels) and antacids (concommitant use results in reduced serum rosuvastatin levels) [48].

CHAPTER 3

3. PAPER 1

Preface

This article has been submitted to the "International Journal of Clinical Pharmacy". The manuscript below was formatted according to author guidelines for this journal. Proof of submission of this manuscript to International Journal of Clinical Pharmacy, comprising of e-mail acknowledging receipt of submission, screenshot of first page of approved PDF, can be found in Appendix 4.

Ethical Clearance documents can be found in Appendix 5.

Title:

The impact of the introduction of generics and generic reference pricing on candesartan and rosuvastatin utilisation, price and expenditure in South Africa

Authors:

de Jager H (B.Pharm)[1], Suleman F (B.Pharm, M.Pharm, Ph.D)[2,3]

Affiliations:

[1,2] Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal (Westville Campus), Private Bag X54001, Durban, 4000, KwaZulu-Natal, South-Africa.

[3] Faculty of Science, Utrecht University, Utrecht, The Netherlands

Job Title:

1. Postgraduate student
2. Associate Professor, Discipline of Pharmaceutical Sciences
3. Professor, and the Prince Claus Chair of Development and Equity for the theme Affordable (Bio)Therapeutics for Public Health (September 2016 to September 2018),

Corresponding author:

Prof Fatima Suleman, Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal – Westville Campus, Private Bag X54001, Durban, 4000. KZN. South Africa

(Tel) +27 31 2607941

(Fax) +27 31 2607792

(Email) sulemanf@ukzn.ac.za

Running Title

The impact of the introduction of generics and generic reference pricing on candesartan and rosuvastatin utilisation, price and expenditure in South Africa

Abstract

Background: In the South African private sector context, generically similar products are grouped together and the reimbursement rate is set at the average price of the generically equivalent products. Very little evidence exists in low and middle-income countries with regards to the impact of this policy over time.

Objectives: To determine the impact of the introduction of generics and generic reference pricing on candesartan and rosuvastatin in the South African private health care sector in terms of medicine utilisation, medicine price and medicine expenditure.

Setting: South African private health sector

Method: Medicine claims for candesartan and rosuvastatin was obtained from a Pharmacy Benefit Manager in South Africa. The claims covered a 48-month period from January 2012 to December 2015 and provided a pre- and post-reference price period for analysis. Medicine utilisation was measured as the number of Defined Daily Doses dispensed per 100 000 beneficiaries. Medicine price and expenditure was calculated as the average per Defined Daily Dose.

Main outcome measure: Medicine utilisation, price and expenditure

Results: Candesartan experienced an average 7.0% year-on-year decline in utilisation and rosuvastatin a 5.0% increase. Medicine expenditure reduced by an additional 34.6% and 20.9% for candesartan and rosuvastatin respectivel. The total savings was 54.8% for candesartan and 31.9% for rosuvastatin.

Conclusion: The introduction of generics and generic reference pricing did not have an impact on medicine utilisation, but reduced the price and expenditure of both candesartan and rosuvastatin.

Key words

Generics, Generic reference pricing, Medicine expenditure, South Africa

Impact of research findings on pharmacy/clinical practice

- Generic substitution and generic reference pricing could reduce medicine expenditure without affecting health outcomes
- Utilisation of generic medicines, after patent expiry, improves over time as more competitors enter the market

Introduction

Pharmaceutical expenditure is still increasing internationally, although growth has slowed down since the mid-2000s [1, 2]. In South Africa, pharmaceutical expenditure in the private sector reached ZAR 22.3 billion in 2015, a 36.8% increase from the ZAR 16.3 billion spent in 2012 [3]. The introduction of new medicines and the increasing demand for existing medicines are the main drivers of pharmaceutical spending [2]. The quantity of medicines consumed has increased over time in many therapeutic classes. Most notably, between 2000 and 2013, the use of antihypertensive medication in Organization for Economic Co-operation and Development (OECD) countries nearly doubled, while the use of cholesterol lowering drugs tripled [1]. In South Africa, a similar trend of increasing consumption can be seen, with hypertension prevalence increasing from 114.6 per 1,000 beneficiaries in 2011 to 152.8 per 1,000 beneficiaries in 2015 [3]. Despite the nominal growth in pharmaceutical expenditure and the increased consumption, pharmaceutical expenditure as a percentage of total health expenditure has reached a plateau [1, 2]. In South Africa, pharmaceutical expenditure contributed 16.1% to overall health expenditure in the private sector in 2015, only marginally more than the 15.8% spent in 2012 [3].

Two factors that contributed to the stagnation in growth of pharmaceutical expenditure is the introduction of generic medicines and the introduction and strengthening of cost-containment policies [1, 4]. Generic medicines offer the opportunity to make substantial savings without affecting the quality of care [5]. The introduction of generic medicines may lower utilisation of more expensive brand name products, which results in savings in pharmaceutical expenditure [2]. In South Africa, generic medicines are on average 22% cheaper than their brand name equivalents, and 56% cheaper than products without any generic competition [6]. Generic medicines were responsible for 56.2% of all drugs dispensed in South Africa in 2015 [6]. One of the cost-containment policies used to promote the use of generic medicines is reference pricing. In essence, reference pricing groups therapeutically similar medicines together and sets

a maximum reimbursement rate for the group of medicines [7]. Any medication with a price below or at the reference price will be covered in full, while medicine with a higher price will only be partially reimbursed with the beneficiary paying the balance between the price of the chosen medicine and the reference price. Reference pricing can change the demand for expensive brand name medicines, when people elect to use cheaper generic alternatives to avoid out-of-pocket co-payments. Reference pricing does not have adverse effects on health outcomes [7, 8]. It also does not increase the use of other health services, with the possible exception of an increase in doctors' consultations when reference pricing is introduced and patients want to switch to cheaper reference medicines [9].

Background to the South African pharmaceutical environment

South Africa is a developing country with limited health care resources [10]. The country has a two-tiered health care system with 8.8 million people (16% of the population) insured by private insurers [3, 11]. A national drug policy (NDP) was established in 1996 which led to the establishment of a pricing committee and the introduction of a Single Exit Price (SEP) on all pharmaceuticals in the private health sector [12, 13]. Mandatory offer of generic substitution was introduced in 2003 which empowered pharmacists to offer to substitute brand name products with a generic equivalent [14]. These changes paved the way for the introduction of generic reference pricing in the private health sector, with the first applications as far back as 2005 [15]

Aim of the study

There are numerous studies analysing the impact of generic medicines on pharmaceutical expenditure, as well as the impact of generic reference pricing on pharmaceutical expenditure. Data from low and middle income countries, like South Africa, however, remain limited. The aim of this study is to determine the impact of the introduction generics and generic reference pricing on candesartan and rosuvastatin, who recently lost their patent protection, in an

environment where generic reference pricing is already applied on other unprotected pharmaceutical products. The impact was measured on medicine utilisation, the average medicine price as well as the impact on medicine expenditure. This study will help answer the question regarding whether reference pricing has longer term benefits after the initial introduction of the reference pricing policy, which usually results in a reduction in medicine expenditure.

Ethical approval

Ethical approval for this study was granted by the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (BREC), reference number BE348/15.

Method

This study is a retrospective longitudinal analysis of a medicine claims database. Medicine claims data was supplied by an independent Pharmacy Benefit Manager (PBM) in South Africa. For the study period, the PBM processed medicine claims for 1.45 million private health care beneficiaries in South Africa. The database includes demographic information about the beneficiaries, including: date of birth, age, and gender. All beneficiary identification numbers were decoded and de-identified to ensure confidentiality. To ensure the reliability and validity of the results, a list of quality criteria for interrupted time series designs was adopted when the research methods and tools were designed [16].

The study period covered a 48-month period from January 2012 to December 2015. Both rosuvastatin and candesartan received generic competition in this period and generic reference pricing was subsequently introduced on the active ingredients. Generic reference pricing was introduced in April 2013 for rosuvastatin, and in February 2014 for candesartan. For both rosuvastatin and candesartan, the study period provided a pre-intervention base where generic reference pricing was not applied, to determine the impact of generic reference pricing after generic alternatives became available.

Only beneficiaries from registered medical schemes who were contracted with the PBM for the entire study period were included in the study population. This was done to control inconsistencies in the before and after comparisons of the introduction of generic reference pricing, because of changes in volume and the make-up of the study population. Of the medical schemes contracted with the PBM for the entire study period, only those who applied generic reference pricing were included in the study population. Medical schemes that had major benefit design changes in the study period, e.g. changes in medicine formulary or other co-payment changes, were excluded from the study. These changes in benefit design could have an impact on the utilisation and expenditure of rosuvastatin and candesartan, not because of the introduction of generics and generic reference pricing.

Changes in medicine utilisation was measured by converting the claimed quantity to Defined Daily Dose (DDD) per 100 000 beneficiaries. DDD represents the assumed mean maintenance dose per day for a medicine when used for its main indication [17]. The standardisation of medicine volume to DDD enables utilisation comparisons across the different strengths of the same active ingredient. To control changes in the study population, the medicine volume was calculated as DDD dispensed per 100 000 beneficiaries, on the basis of the membership data of the medical schemes included in the study population.

All medicine prices were obtained from the South African Medicine Price Registry, Database of Medicine Prices [18]. Prices are expressed in South African Rand (ZAR) and were adjusted to the year in which generic reference pricing was first introduced on the active ingredient. The Single Exit Price Adjustment (SEPA) published in the South African Government Gazette was used to adjust the prices according to the year in which the product was dispensed [6]. Prices for candesartan are expressed in ZAR 2014 (Q2) and rosuvastatin in ZAR 2013 (Q1). Prices excludes dispensing fee and sales tax (value added tax (VAT) in South Africa). Price was calculated by multiplying the volume sold with the adjusted SEP and dividing by the number of DDD dispensed. Price therefore always refers to the price per DDD of the active ingredient.

Medicine expenditure was calculated by multiplying the medicine price with the volume utilised and subtracting the patient out-of-pocket co-payments because of the application of generic reference pricing.

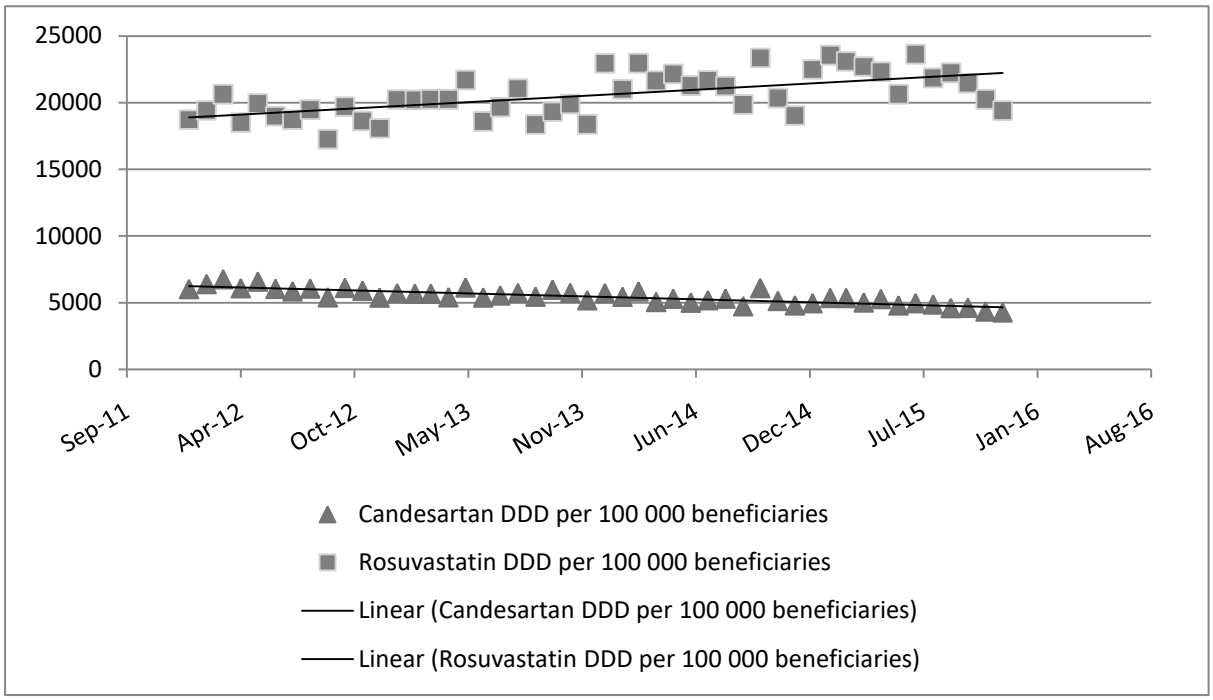
Results

The characteristics of the 1 444 beneficiaries using candesartan, and the 10 452 beneficiaries using rosuvastatin were stable during the 48-month study period. For candesartan, 765 beneficiaries had claims in both the pre- and post-reference price periods, and for rosuvastatin 4 738 beneficiaries claimed in both periods. Women represented 46% of the beneficiaries for the candesartan group and 43% of the rosuvastatin group. The mean age was 65.0 (standard deviation 12.3 years) and 61.2 years (standard deviation 11.5 years) for the candesartan and rosuvastatin groups respectively.

Medicine Utilisation

Candesartan experienced a 19.6% reduction in DDD dispensed per 100 000 beneficiaries over the study period, or an average 7.0% year-on-year change over the four years. Rosuvastatin experienced a 15.6% increase in DDD dispensed per 100 000 beneficiaries over the study period, or an average 5.0% year-on-year over the four years. As illustrated in Figure 1, the change in the number of DDD dispensed per 100 000 beneficiaries was a gradual change over time for both candesartan and rosuvastatin and was not caused by a big shift because of the introduction of generics and generic reference pricing.

Figure 1 Candesartan and rosuvastatin utilisation for the period January 2012 to December 2015



Although the overall number of DDD dispensed per 100 000 beneficiaries was not affected by the introduction of generics and generic reference pricing, there was a significant change in the mix of original brand name products versus generic alternatives dispensed after the introduction of generics and generic reference pricing. The initial uptake of generic equivalents in the year of the introduction of generic reference pricing was significant, and increased even further in subsequent years. For candesartan, the generic utilisation reached 47.4% in the year of the introduction of generic reference pricing, and grew further to 59.3% in the following year. Generic utilisation of rosuvastatin started at 24.0% in the year of the introduction of generic reference pricing, and increased to 63.9% in the subsequent year and 76.4% in the year thereafter. Figure 2 illustrates the change in the mix of original brand name products and generic equivalents over the study period.

Figure 2 Candesartan utilisation of original brand name product and generic alternatives, measured in DDD per 100 000 beneficiaries

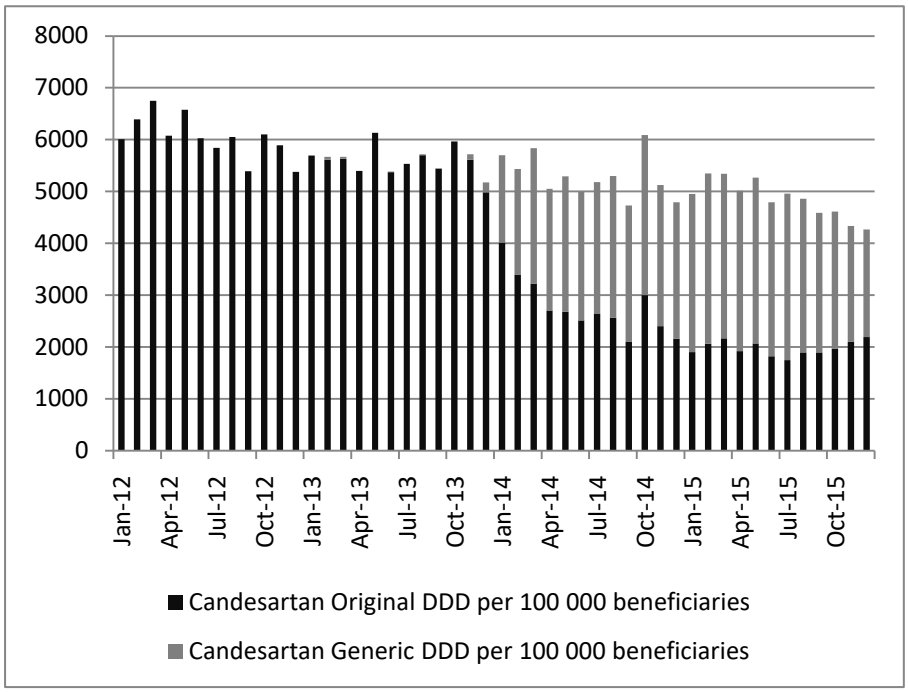
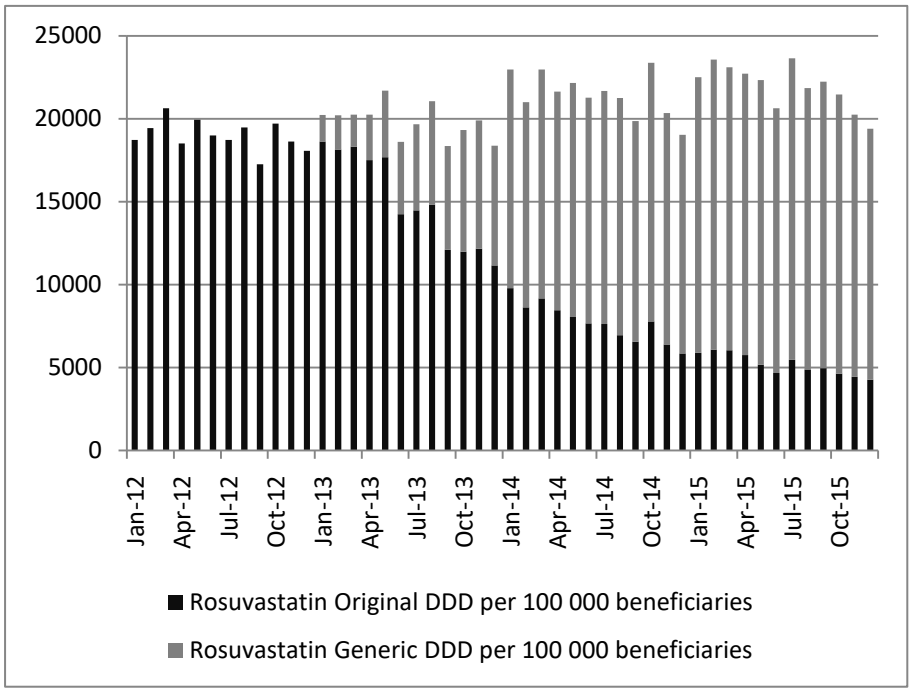


Figure 3 Rosuvastatin utilisation of original brand name product and generic alternatives, measured in DDD per 100 000 beneficiaries



Medicine Price

Average price reductions range from 13.9% to 31.0% for rosuvastatin and candesartan respectively. The average price per DDD for candesartan reduced from ZAR 4.28 to ZAR 2.96, while the average price per DDD for rosuvastatin decreased from ZAR 8.06 to ZAR 6.94 in the study period. The magnitude of the difference in price between the original brand name product compared to the average price of the generic equivalents was much greater for candesartan compared to rosuvastatin. For candesartan, the average generic equivalent product is 54.5% cheaper than the original brand name product, while the difference in price for rosuvastatin was only 24.9%.

Table 1 Candesartan and rosuvastatin price (in ZAR) and expenditure (in ZAR) per DDD

	Candesartan			Rosuvastatin		
	Pre RP[1]	**Post RP[2]**	**Saving**	**Pre RP[3]**	**Post RP[4]**	**Saving**
Average Price per DDD	4.28	2.96	31.0%	8.06	6.94	13.9%
Original Brand Price per DDD	4.32	4.20	2.8%	8.08	8.20	-1.6%
Average Generic Price per DDD	N/A[5]	1.91	N/A[5]	N/A[5]	6.16	N/A[5]
Average Expenditure per DDD	4.28	1.93	54.8%	8.06	5.49	31.9%
Price Saving per DDD		1.33	**31.0%**		1.12	**13.9%**
Reference Price Saving per DDD		1.02	**34.6%**		1.45	**20.9%**
Total Saving per DDD		2.35	**54.8%**		2.57	**31.9%**

[1]*The pre-reference price period for candesartan was from January 2012 to January 2014*

[2] *The post-reference price period for candesartan was from February 2012 to December 2015*

[3] *The pre-reference price period for rosuvastatin was from January 2012 to March 2013*

[4] *The post-reference price period for rosuvastatin was from April 2013 to December 2015*

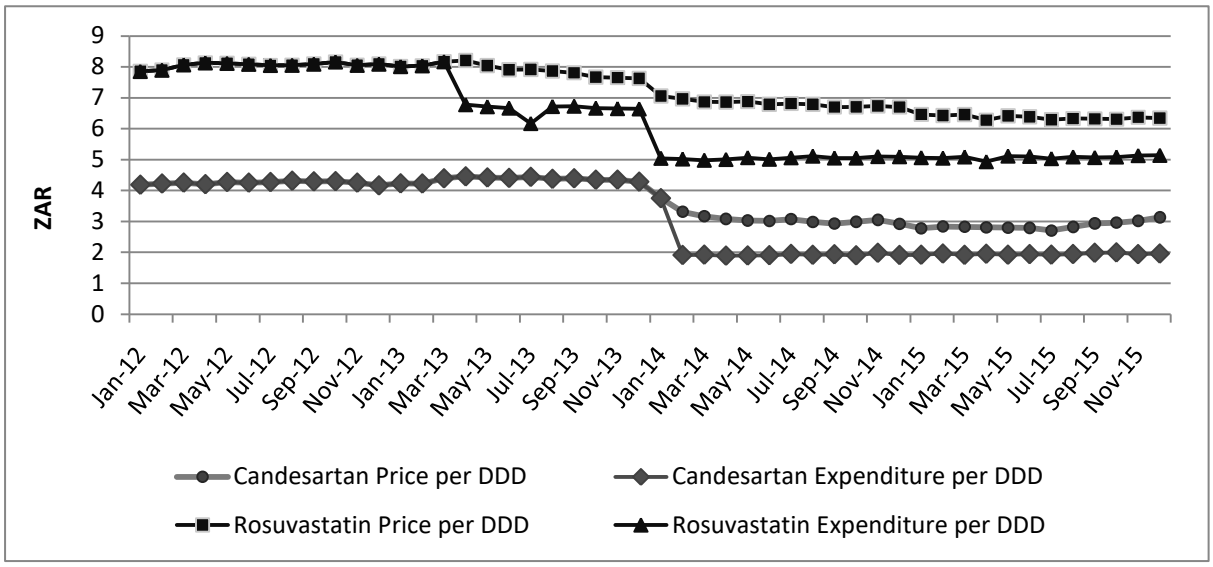
[5]*There were no generic equivalent products available in the pre-reference price period. As a result, the average price per DDD and saving could not be calculated*

Medicine expenditure

The introduction of generic reference pricing produced an additional saving on medicine expenditure of 34.6% for candesartan and 20.9% for rosuvastatin. This saving is in addition to the 31.0% and 13.9% saving that resulted from the reduction in price per DDD because of the introduction of generic equivalents. Candesartan expenditure decreased from ZAR 4.28 to ZAR 1.93 per DDD after the intervention. Rosuvastatin expenditure decreased from ZAR 8.06 to ZAR 5.49 per DDD. The application of generic reference pricing resulted in a reference price co-payment of ZAR 1.02 per DDD for candesartan and ZAR 1.45 per DDD for rosuvastatin. Figure 3 illustrates the additional impact of generic reference pricing on medicine expenditure after the introduction of the reference price in February 2014 for candesartan, and April 2013 for rosuvastatin.

The total saving in medicine expenditure per DDD is 54.8% for candesartan and 31.9% for rosuvastatin. This equates to a saving of ZAR 1.4 million for candesartan and ZAR 8.8 million for rosuvastatin during the post-reference price period in the study.

Figure 4 Candesartan and rosuvastatin price and expenditure per DDD for the period January 2012 to December 2015



[1] *Generic reference pricing for candesartan was introduced in February 2014*

[2] *Generic reference pricing for rosuvastatin was introduced in April 2013*

[3] *In the period March 2013 to December 2013 there was only one generic equivalent product available for rosuvastatin, distributed by the same manufacturer as the original brand name product*

Discussion

Hypertension and hyperlipidaemia remain two of the most prevalent non-communicable diseases in the South African health care landscape. According to the 2015 Mediscor Medicines Review (MMR), antihypertensives was the top therapeutic group according to medicine expenditure, while the hypolipidaemic agents were ranked sixth [6]. In 2012, a year prior to the introduction of generics and generic reference pricing, the various strengths of brand name rosuvastatin occupied two places in the list of top 20 products according to expenditure (6th and 12th).

The introduction of generics and generic reference pricing did not change the overall utilisation of either candesartan or rosuvastatin. It did however have an impact on the mix of original brand name products and generic equivalents that were claimed in the post-reference price period. The

higher generic uptake for rosuvastatin can be ascribed to a longer post-reference price period, greater number of generic competitors during this period, and the introduction of a clone product by the manufacturer of the original brand name product. The high initial generic uptake of both candesartan and rosuvastatin is because of the practice of both generic substitution (since 2003) and generic reference pricing on other classes of pharmaceutical products.

The greater number of generics and generic uptake for rosuvastatin did not result in greater savings in price per DDD in the post-reference price period. The price per DDD for rosuvastatin decreased by 13.9%, while candesartan experienced a 31.0% reduction. The greater savings in price per DDD for candesartan is a result of a greater price difference between the original brand name product and the average price of generic equivalents. For candesartan, the average price of the generic equivalent products was 54.5% cheaper than the brand name product, while for rosuvastatin the difference was only 24.9%. The price difference for rosuvastatin is however somewhat diluted, because for the first six months after the introduction of reference pricing there was only one generic equivalent product available, distributed by the same manufacturer as the original brand name product at a 19.7% discount. In the following 24 months, an additional three competitor generic equivalent products were launched, and the premium on the brand name product increased to 27.0% compared to the average generic price. The difference between the price of the original brand name product and the generic equivalents is not as big as seen in other countries in the world [1, 2, 9]. This could possibly be because of a smaller number of generic competitors in the South African market as well as the price controls enforced through the SEP legislation.

The reduction in the average price per DDD is solely contributed to the introduction of generic alternatives. Although it is possible that reference pricing had an influence on the decision of beneficiaries to move to a generic alternative, this study cannot correlate the change directly to reference pricing because beneficiaries did not have the opportunity to choose a generic alternative before the introduction of reference pricing. The introduction of reference pricing

did, however, result in reductions in the expenditure per DDD because of the out-of-pocket co-payments experienced by members who elected to use a product above the reference price. It can be argued that this additional saving is only a saving to the insurer and not a saving to overall health care expenditure, because beneficiaries will be responsible for out-of-pocket co-payments. Further research is required as to how many beneficiaries opted for the additional out-of-pocket expenditure and why. Candesartan experienced an additional 34.6% saving on the expenditure per DDD because of the introduction of reference pricing, resulting in an overall saving of 54.8% per DDD. Rosuvastatin had an additional saving of 20.9% in expenditure per DDD, resulting in an overall saving of 31.9%.

Conclusion

Generic reference pricing offers the ability to generate additional savings in pharmaceutical expenditure in the longer term, as more original brand name products lose their patent protection and generic alternatives are introduced in the market. This study only focussed on the private health care market in South Africa, and the impact on the public health sector still needs to be determined. Further studies are needed on more products as well as the impact on the entire therapeutic class to ensure that beneficiaries aren't switching to other products not affected by reference pricing.

Conflicts of interest: None

References

1. OECD Indicators. Health at a Glance 2015. OECD Indicators, OECD Publishing, Paris. DOI: https://doi. org/10.1787/health_glance-2015-en. Accessed February 2015; 15:2016.

2. Institute QuintilesIMS. Understanding the dynamics of drug expenditure: A review of selected countries, 1995-2015 [Internet]. USA: QuintilesIMS Institute; 2017 [cited 2017 Aug 9]. Available from: http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/understanding-the-dynamic-composition-of-drug-expenditure.

3. Council for Medical Schemes. Annual Report, 2012-2013. Pretoria: Council for Medical Schemes, 2013.

4. Vogler S, Zimmermann N, Leopold C, de Joncheere K. Pharmaceutical policies in European countries in response to the global financial crisis. Southern Med Review. 2011;4(2):69-79.

5. Manzoli L, Flacco ME, Boccia S, D'Andrea E, Panic N, Marzuillo C, et al. Generic versus brand-name drugs used in cardiovascular disease. European Journal of Epidemiology. 2016; 31(4):351-68.

6. Bester M, Badenhorst C, Greeff J, De Jager H. Mediscor Medicines Review 2015 [Internet]. Centurion: Mediscor PBM; 2016 [cited 2017 Aug 9]. Available from: http://www.mediscor.co.za/mediscor-medicine-review/.

7. Aaserud M, Dahlgren AT, Kösters JP, Oxman AD, Ramsay C, Sturm H. Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies. Cochrane Database of Systematic Reviews. 2006;2: CD005979..

8. Lee IH, Bloor K, Hewitt C, Maynard A. International experience in controlling pharmaceutical expenditure: influencing patients and providers and regulating industry - a systematic review. Journal of health services research & policy. 2015;20(1):52-9.

9. Grootendorst PV, Dolovich LR, Holbrook AM, O'Brien BJ. The impact of reference pricing of cardiovascular drugs on health care costs and health outcomes: evidence from British Columbia. Report for the Canadian Health Services Research Foundation. 2001.

10. United Nations. Country classification, 2014. Available from: *http://www.un.org/en/development/desa/policy/wesp/wesp_current/2014wesp_country_classification.pdf*

11. Statistics South Africa. Mid-year population estimates, 2015. Pretoria: Statistics South Africa. 2016. Available from: https://www.statssa.gov.za/publications/P0302/P03022015.pdf.

12. Department of Health. National Drug Policy for South Africa [Internet]. Department of Health, Pretoria; 1996. [cited 2017 Sep 2]. Available from: http*://www.gov.za/documents/national-drugs-policy*.

13. Republic of South Africa. Medicines and Related Substances Control Act (No. 101 of 1965), as amended. Available from: *http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/legislations/acts/medicines_and_related_sub_act_101_of_1965.pdf*

14. Gray AL. Medicine Pricing Interventions – the South African experience. Southern Med Review. 2009;2(2):15-19.

15. Bester M, Hamman E. Mediscor Medicines Review 2005 [Internet]. Centurion: Mediscor PBM; 2016 [cited 2017 Aug 20]. Available from: http://www.mediscor.co.za/mediscor-medicine-review/.

16. Ramsey CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. International journal of technology assessment in health care. 2003;19(4):613-23.

17. World Health Organization. Guidelines for ATC classification and DDD assignment, WHO Collaborating Centre for Drug Statistics Methodology. Oslo: Nordic Council on Medicines. 1999.

18. South African Medicine Price Registry. Database of medicine prices 9 July 2017. Available from http://www.mpr.gov.za/.

CHAPTER 4

4. SUMMARISED RECOMMENDATIONS AND CONCLUSION

4.1 Recommendations

The introduction of generic medicines, generic substitution and reference pricing are effective policies to shift medicine utilisation away from expensive originator medicine to more cost effective generic reference medicines. South Africa, in an effort to create a transparent pricing system and reduce the cost of medicine, might have legislated some of the medicine expenditure savings, out of these policies. The utilisation of generic medicines in South Africa compares favourably with utilisation rates of some countries in Europe, but we are still lagging behind the leading countries like the US, UK and Germany. Unfortunately, because of the relatively high price of our generic medicines, we are not realising the same medicine expenditure savings as other countries.

The introduction of level 1 generic reference pricing in South Africa has had a positive impact on medicine expenditure. If the reference groups are expanded to level two, where medicines in the same therapeutic class are referenced together, even greater savings can be achieved. The risk of adverse events in level two reference pricing is greater when switching medicines (compared to level 1 reference pricing), but by avoiding high risk therapeutic groups like antiepileptic drugs, this risk can be managed and greater savings can be achieved.

The implementation of a reference pricing policy seems to have longer term benefits, than just the initial reduction in price after implementation of the policy. As demonstrated by candesartan and rosuvastatin in South Africa, reference pricing could also lead to future medicine expenditure savings as more originator medicines lose their patent protection and generic medicines are introduced to the market. With the current international trend of increasing medicine consumption due to an ageing population, these policies will play a critical role in ensuring that medicines remain affordable and accessible to all.

4.2 Conclusion

This study revealed that the introduction of generics and generic reference pricing is effective in changing utilisation towards lower cost generic equivalent medicines. For candesartan and rosuvastatin in South Africa, the change in generic utilisation rate caused a reduction in both the price of medicine, as well as the pharmaceutical expenditure by third party payers. Although the results are positive, the magnitude of the savings can be improved by further lowering the price of generic equivalent products to rates that are comparable to international reference prices and by expanding the reference groups to level 2 therapeutic groups. To be able to generalise the results of this study to all medicines in South Africa, the impact analysis will have to be expanded to include all medicines within the therapeutic class as well as expand the selection to more therapeutic classes.

REFERENCES FOR INTRODUCTION AND LITERATURE REVIEW

1. OECD Indicators. Health at a Glance 2015. OECD Indicators, OECD Publishing, Paris. DOI: https://doi. org/10.1787/health_glance-2015-en. Accessed February 2015; 15:2016.
2. QuintilesIMS Institute. Understanding the dynamics of drug expenditure: A review of selected countries, 1995-2015 [Internet]. USA: QuintilesIMS Institute; 2017 [cited 2017 Aug 9]. Available from: http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/understanding-the-dynamic-composition-of-drug-expenditure.
3. Council for Medical Schemes. Annual Report, 2012-2013. Pretoria: Council for Medical Schemes, 2013.
4. Vogler S, Zimmermann N, Leopold C, de Joncheere K. Pharmaceutical policies in European countries in response to the global financial crisis. Southern Med Review. 2011;4(2):69-79.
5. Bester M, Badenhorst C, Greeff J, De Jager H. Mediscor Medicines Review 2015 [Internet]. Centurion: Mediscor PBM; 2016 [cited 2017 Aug 9]. Available from: http://www.mediscor.co.za/mediscor-medicine-review/.
6. Manzoli L, Flacco ME, Boccia S, D'Andrea E, Panic N, Marzuillo C, et al. Generic versus brand-name drugs used in cardiovascular disease. European Journal of Epidemiology. 2016; 31(4):351-68.
7. Aaserud M, Dahlgren AT, Kösters JP, Oxman AD, Ramsay C, Sturm H. Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies. Cochrane Database of Systematic Reviews. 2006;2: CD005979.
8. Bester M, Hamman E. Mediscor Medicines Review 2005 [Internet]. Centurion: Mediscor PBM; 2016 [cited 2017 Aug 20]. Available from: http://www.mediscor.co.za/mediscor-medicine-review/.
9. Lee IH, Bloor K, Hewitt C, Maynard A. International experience in controlling pharmaceutical expenditure: influencing patients and providers and regulating industry - a systematic review. Journal of health services research & policy. 2015;20(1):52-9.
10. Grootendorst PV, Dolovich LR, Holbrook AM, O'Brien BJ. The impact of reference pricing of cardiovascular drugs on health care costs and health outcomes: evidence from British Columbia. Report for the Canadian Health Services Research Foundation. 2001.
11. Trochim WM, Donnely JP. Research methods knowledge base. 2001.
12. Ander-Peciva S. Constructin of longitudinal databases - for flexibility, transparency, and longevity. In meeting of the International Commission for Historical Demography. 2005.
13. Ramsey CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. International journal of technology assessment in health care. 2003;19(4):613-23.
14. Dunne S, Shannon B, Dunne C, Cullen W. A review of the difference s and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacology and Toxicology. 2013; 14:1.
15. Colombo GL, Agabiti-Rosei E, Margonato A, Mencacci C, Montecucco CM, Trevisan R. Off-patent generic medicines vs. off-patent brand medicines for six reference drugs:

A retrospective claims data study from five local healthcare units in the Lombardy region of Italy. PLos ONE. 2013; 8(12): e82990.
16. Gothe H, Schall I, Saverno K, Mitrovic M, Luzak A, Brixner D. The impact of generic substitution on health and economic outcomes: a systematic review. Appl Health Econ Health Policy. 2015; 13(1):S21-S33.
17. Walker R, Kanfer I, Skinner MF. Bioequivalence Assessment of Generic Products: An Innovative South African Approach. Clinical Research and Regulatory Affairs. 2008; 23:11-20.
18. Patel A, Gauld R, Norris P, Rades T. Quality of generic medicines in South Africa: perceptions versus reality - a qualitative study. BMC Health Services Research. 2012; 12(297).
19. Pechlivanoglou P, van der Veen WJ, Bos JH, Postma MJ. Analyzing generic and branded substitution patterns in the Netherlands using prescription data. BMC Health Services Research. 2011; 11(89).
20. Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudry NK, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review. JAMA. 2008; 300(21): 2514-2526.
21. Cooper-deHoff RM, Elliot WJ. Generic drugs for hypertension: are they really equivalent? Curr Hypertens Rep. 2013; 15(4): 340-345.
22. Kesselheim AS, Stedman MR, Bubrick EJ, Gagne JJ, Misono AS, Lee JL, et al. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs. Drugs. 2010; 70(5): 605-621.
23. Kaplan WA, Wirtz VJ, Stephens P. The market dynamics of generic medicines in the private sector of 19 low and middle income countries between 2001 and 2011: A descriptive time series analysis. PLoS ONE. 2013; 8(9): e74399.
24. Duerden MG, Hughes DA. Generic and therapeutic substitutions in the UK: are they a good thing? British Journal of Clinical Pharmacology. 2010; 70(3): 335-341.
25. Sheingold S, Nguyen NX. Impacts of generic competition and benefit management practices on spending for prescription drugs: evidence from Medicare's Part D benefit. Medicare & Medicaid Research Review. 2014; 4(1): E1-E13.
26. Zeng W. A price and use comparison of generics versus originator cardiovascular medicines: a hospital study in Chongqing, China. BMC Health Services Research. 2013; 13(390).
27. Vogler S, Kilpatrick K, Babar Z. Analysis of medicine prices in New Zealand and 16 European countries. Value in Health. 2015; 18: 484-492.
28. Bangalee V, Suleman F. Has the increase in the availability of generic drugs lowered the price of cardiovascular drugs in South Africa? Health SA Gesondheid. 2016; 21:60-66.
29. Clark B, DuChane J, Hou J, Rubinstein E, McMurray J, Duncan I. Evaluation of increased adherence and cost savings of an employer value-based benefits program targeting generic antihyperlipidemic and antidiabetic medications. J Manag Care Pharm. 2014; 20(2):141-150.
30. Schneeweiss S. Reference drug programs: effectiveness and policy implications. Health Policy. 2007; 81(1): 17-28.

31. Drummond M, Jonsson B, Rutten F, Stargardt T. Reimbursement of pharmaceuticals: reference pricing versus health teachnologyassesment. Eur J Health Econ. 2011; 12: 263-271.
32. Vrijens F, Van de Voorde C, Farfan-Portet MI, Vander Stichele R. Patient socioeconomic determinants for the choice of the cheapest molecule within a cluster, Belgian prescription data. Eur J Health Econ. 2012; 13(3):315-25.
33. Lee JL, Fischer MA, Shrank WH, Polinski JM, Choudry NK. A systematic review of reference pricing: implications for US prescription drug spending. American Journal of Managed Care. 2012; 18(11): e429-e437.
34. McManus P, Birkett DJ, Dudley J, Stevens A. Impact of the Minimum Pricing Policy and introduction of brand (generic) substitution into the Pharmaceutical Benefits Scheme in Australia. Pharmacoepidemiology and Drug Safety. 2001; 10: 295-300.
35. Marshall JK, Grootendorst PV, O'Brien BJ, Dolovich LR, Holbrook AM, Levy AR. Impact of reference-based pricing for histamine-2 receptor antagonists and restricted access for proton pump inhibitors in British Columbia. CMAJ. 2002;166(13):1655-1662.
36. Grootendorst PV, Marshall JK, Holbrook AM, Dolovich LR, O'Brien BJ, Levy AR. The Impact of reference Pricing of nonsteroidal anti-inflammatory agents on the use and costs of analgesic drugs. Canadian Health Services Research Foundation. 2005; 40: 1297-1317.
37. Andersson K, Petzold MG, Sonesson C, Lonroth K,Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug prices? Interrupted time series analysis of cost, volume and cost per volume trends in Sweden 1986 - 2002. Health Policy. 2006; 79: 231-243.
38. Rothberg AD, Blignault J, Serfontein CB, Valodia B, Eekhout S, Pels LM. Experience of a medicine reference-pricing model. South African Medical Journal. 2004; 94(3): 183-188.
39. Pavcnik N. Do pharmaceutical prices respond to potential patient out-of-pocket expenses? RAND Journal of Economics. 2002: 469-487.
40. Grootendorst PV, Dolovich LR, O'Brien BJ, Holbrook AM, Levy AR, . The impact of reference-based pricing of nitrates on the use and costs of anti-anginal drugs. Canadian Medical Association Journal. 2001; 165(8): 1011-1019.
41. United Nations. Country classification, 2014. Available from: http://www.un.org/en/development/desa/policy/wesp/wesp_current/2014wesp_country_classification.pdf
42. Statistics South Africa. Mid-year population estimates, 2015. Pretoria: Statistics South Africa. 2016. Available from: https://www.statssa.gov.za/publications/P0302/P03022015.pdf.
43. Department of Health. National Drug Policy for South Africa [Internet]. Department of Health, Pretoria; 1996. [cited 2017 Sep 2]. Available from: http://www.gov.za/documents/national-drugs-policy.
44. Republic of South Africa. Medicines and Related Substances Control Act (No. 101 of 1965), as amended. Available from: http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/legislations/acts/medicines_and_related_sub_act_101_of_1965.pdf

45. Gray AL. Medicine Pricing Interventions – the South African experience. Southern Med Review. 2009;2(2):15-19. Gray AL. Medicine Pricing Interventions – the South African experience. Southern Med Review. 2009;2(2):15-19.
46. Furst DE, Munster T, Katzung BG. Basic and clinical pharmacology. New York, Mc Graw-Hill, edn. 2001;8:598.
47. Gibbon CJ, editor. South African medicines formulary. Health and Medical Publishing Group; 2012.
48. Husain A, Azim M, Mitra M, Bhasin PS. A Review on Candesartan: Pharmacological and Pharmaceutical Profile. Journal of applied pharmaceutical science. 2011; 01(10):12-17.
49. McTaggart F. Comparative pharmacology of rosuvastatin. Atherosclerosis Supplements. 2003; 4(1):9-14.
50. Luvai A, Mbagaya W, Hall AS, Barth JH. Rosuvastatin: a review of the pharmacology and clinical effectiveness in cardiovascular disease. Clinical Medicine Insights: Cardiology. 2012;6:17-33

APPENDICES

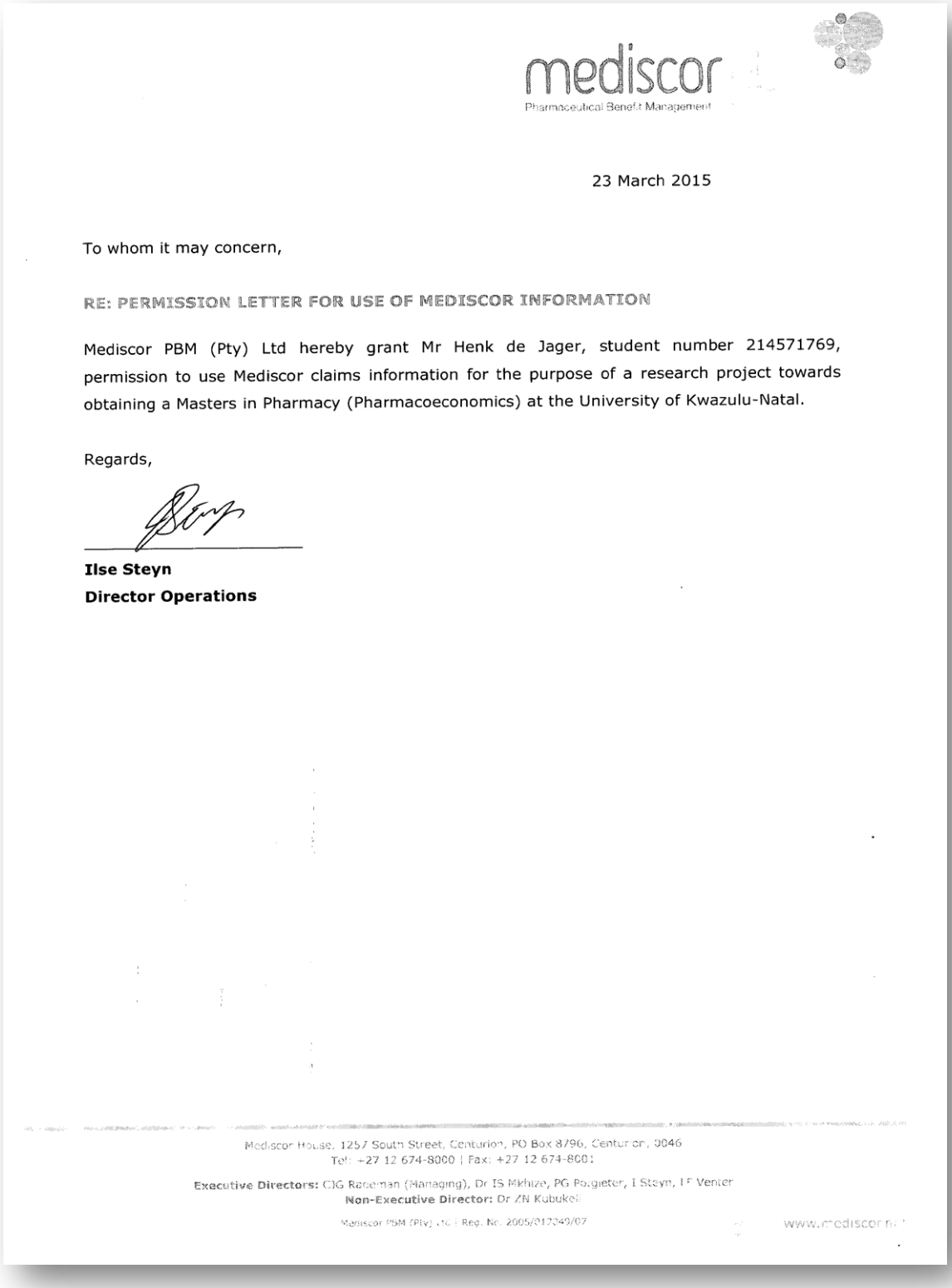
APPENDIX 1

Table 2 Longitudinal database fields and descriptions

Field description
Decoded claims identification number
Claim submit date
Date of service
Provider number
Provider name
Provider discipline (speciality)
Decoded member identification number
Gender
Date of birth
Product identification code
Product name
Generic indicator
Manufacturer code
Manufacturer name
Claim quantity
SEP unit price
Reference price
Scheme amount due
Reference price co-payment

APPENDIX 2

PBM permission letter



mediscor
Pharmaceutical Benefit Management

23 March 2015

To whom it may concern,

RE: PERMISSION LETTER FOR USE OF MEDISCOR INFORMATION

Mediscor PBM (Pty) Ltd hereby grant Mr Henk de Jager, student number 214571769, permission to use Mediscor claims information for the purpose of a research project towards obtaining a Masters in Pharmacy (Pharmacoeconomics) at the University of Kwazulu-Natal.

Regards,

Ilse Steyn
Director Operations

Mediscor House, 1257 South Street, Centurion, PO Box 8796, Centurion, 0046
Tel: +27 12 674-8000 | Fax: +27 12 674-8001

Executive Directors: CIG Raceman (Managing), Dr IS Mkhize, PG Potgieter, I Steyn, LF Venter
Non-Executive Director: Dr ZN Kubukeli

Mediscor PBM (Pty) Ltd | Reg. No. 2005/012049/07 www.mediscor.co.

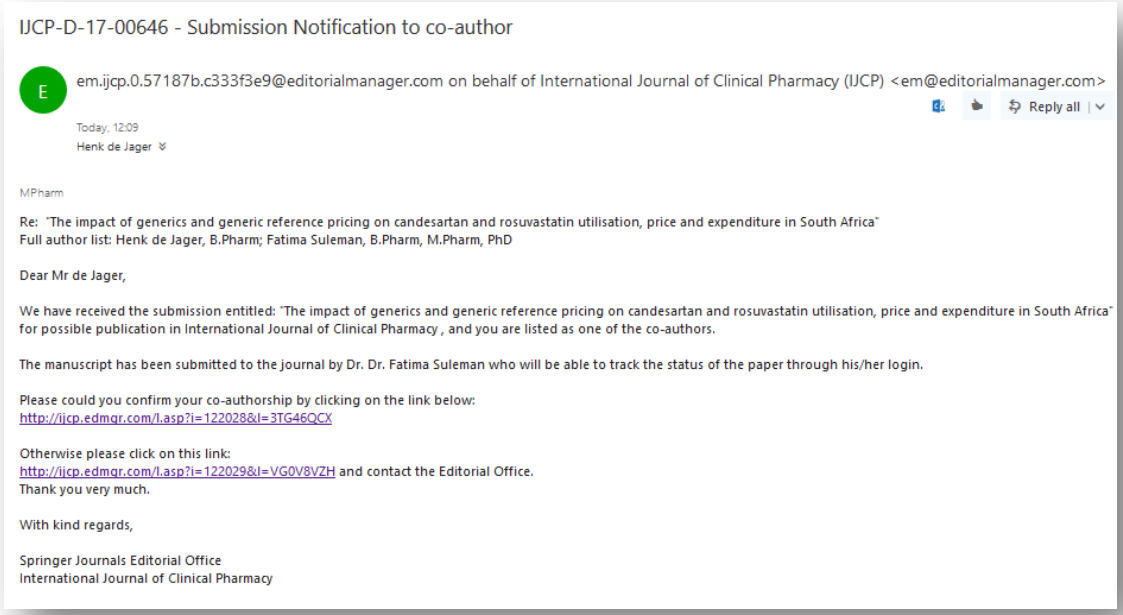
APPENDIX 3

Table 3 Quality criteria for ITS designs

Criteria	**Application**
Intervention occurred independently of other changes over time	Third party payers who introduced any other benefit design changes on rosuvastatin and candesartan were excluded from the study
Intervention was unlikely to affect data collection	Data was collected retrospectively, after the introduction of reference pricing
The primary outcome was assessed blindly or was measured objectively	All four of the study outcomes (medicine cost, medicine volume, medicine expenditure and out-of-pocket payments) can be measured objectively for both the pre-and-post intervention measures
The primary outcome was reliable or was measured objectively	Outcome measurement is objective, change in slope of linear regression line
The composition of the data set at each point covered at least 80% of the total number of participants in the study	All participants who qualify for the study according to the inclusion criteria will be included in the longitudinal database covering the 48 months of the study
The shape of the intervention effect was pre-specified	A change in the slope of the linear regression line is expected
The study was analysed appropriately using time series techniques	Time series regression models will be used to analyze the data

APPENDIX 4

Acknowledgement of receipt of submission



IJCP-D-17-00646 - Submission Notification to co-author

E em.ijcp.0.57187b.c333f3e9@editorialmanager.com on behalf of International Journal of Clinical Pharmacy (IJCP) <em@editorialmanager.com>

Reply all

Today, 12:09

Henk de Jager

MPharm

Re: "The impact of generics and generic reference pricing on candesartan and rosuvastatin utilisation, price and expenditure in South Africa"
Full author list: Henk de Jager, B.Pharm; Fatima Suleman, B.Pharm, M.Pharm, PhD

Dear Mr de Jager,

We have received the submission entitled: "The impact of generics and generic reference pricing on candesartan and rosuvastatin utilisation, price and expenditure in South Africa" for possible publication in International Journal of Clinical Pharmacy , and you are listed as one of the co-authors.

The manuscript has been submitted to the journal by Dr. Dr. Fatima Suleman who will be able to track the status of the paper through his/her login.

Please could you confirm your co-authorship by clicking on the link below:
http://ijcp.edmgr.com/l.asp?i=122028&l=3TG46QCX

Otherwise please click on this link:
http://ijcp.edmgr.com/l.asp?i=122029&l=VG0V8VZH and contact the Editorial Office.
Thank you very much.

With kind regards,

Springer Journals Editorial Office
International Journal of Clinical Pharmacy

APPENDIX 5

BREC approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

23 October 2015

Mr H de Jager (214571769)
Discipline of Pharmaceutical Sciences
School of Health Sciences
henk@mediscor.co.za

Protocol: The impact of reference pricing on rosuvastatin and candesartan on pharmaceutical expenditure: an interrupted time series study of medicine claims data in South Africa.
Degree: MPharm
BREC reference number: BE348/15

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 31 July 2015.

The conditions have been met and the study is given full ethics approval.

This approval is valid for one year from **23 October 2015.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **10 November 2015.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: sulemanf@ukzn.ac.za
cc postgrad: nenep1@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

APPENDIX 6

Table 4 Candesartan descriptive statistics of study population

Statistic	Pre RP	Post RP	Total
Total claim lines	14063	11794	25857
No of unique beneficiaries	1113	960	1444
No of beneficiaries that claimed in pre and post RP periods			765
Ben average age	64.58	65.43	64.97
Ben median age	65.02	65.60	65.33
Ben mode age	71.83	56.15	66.38
Age variance	147.73	152.57	150.11
Age std dev	12.15	12.35	12.25
Female	0.46	0.46	0.46
Male	0.54	0.54	0.54
Age 19-29	0.001484	0.001014	0.00127
Age 30-39	0.022337	0.018165	0.020436
Age 40-49	0.081925	0.071765	0.079552
Age 50-59	0.249947	0.238256	0.244621
Age 60-69	0.277161	0.288189	0.282185
Age 70-79	0.255248	0.241298	0.248894
Age 80-89	0.102283	0.122677	0.111573
Age 90-99	0.009613	0.013687	0.011469

APPENDIX 7

Table 5 Rosuvastatin descriptive statistics of study population

Statistic	Pre RP	Post RP	Total
Total claim lines	53124	138907	192031
No of unique beneficiaries	5930	9261	10452
No of beneficiaries that claimed in pre and post RP periods			4738
Ben average age	60.46	61.49	61.20
Ben median age	60.61	61.61	61.34
Ben mode age	61.45	61.99	61.99
Age variance	131.19	133.54	133.10
Age std dev	11.45	11.56	11.54
Female	0.43	0.43	0.43
Male	0.57	0.57	0.57
Age 19-29	0.008301	0.007055	0.0074
Age 30-39	0.024659	0.0229	0.023387
Age 40-49	0.131937	0.116682	0.120902
Age 50-59	0.295667	0.28401	0.287235
Age 60-69	0.317427	0.318364	0.318105
Age 70-79	0.180465	0.196772	0.192261
Age 80-89	0.039304	0.050782	0.047607
Age 90-99	0.00224	0.003434	0.003104

APPENDIX 8

Table 6 Candesartan SEP comparison: January 2012 to December 2015

Month	Atacand 16mg	Mylacand 16mg	Candagen 16mg	Mediscor Reference Price
January 2012	6.69393			
February 2012	6.69393			
March 2012	6.83714			
April 2012	6.83714			
May 2012	6.83714			
June 2012	6.83714			
July 2012	6.83714			
August 2012	6.83714			
September 2012	6.83714			
October 2012	6.83714			
November 2012	6.83714			
December 2012	6.83714			

Month	Atacand 16mg	Mylacand 16mg	Candagen 16mg	Mediscor Reference Price
January 2013	6.83714			
February 2013	6.83714			
March 2013	7.23357			
April 2013	7.23357			
May 2013	7.23357			
June 2013	7.23357			
July 2013	7.23357			
August 2013	7.23357			
September 2013	7.23357			
October 2013	7.23357	3.03800		
November 2013	7.23357	3.03800		
December 2013	7.23357	3.03800		

Month	Atacand 16mg	Mylacand 16mg	Candagen 16mg	Mediscor Reference Price
January 2014	7.23357	3.03800		
February 2014	7.23357	3.03800		3.04000
March 2014	7.23357	3.03800		3.04000
April 2014	7.23357	3.03800		3.04000
May 2014	7.23357	3.03800		3.04000
June 2014	7.23357	3.21467		3.04000
July 2014	7.23357	3.21467	3.03800	3.22000
August 2014	7.23357	3.21467	3.03800	3.22000
September 2014	7.23357	3.21467	3.03800	3.22000
October 2014	7.23357	3.21467	3.03800	3.22000
November 2014	7.23357	3.21467	3.03800	3.22000
December 2014	7.23357	3.21467	3.03800	3.22000

Month	Atacand 16mg	Mylacand 16mg	Candagen 16mg	Mediscor Reference Price
January 2015	7.23357	3.21467	3.03800	3.22000
February 2015	7.23357	3.21467	3.03800	3.22000
March 2015	7.77607	3.21467	3.03800	3.22000
April 2015	7.77607	3.45600	3.26600	3.22000
May 2015	7.77607	3.45600	3.26600	3.46000
June 2015	7.77607	3.45600	3.26600	3.46000
July 2015	7.77607	3.45600	3.26600	3.46000
August 2015	7.77607	3.45600	3.26600	3.46000
September 2015	7.77607	3.45600	3.26600	3.46000
October 2015	7.77607	3.45600	3.26600	3.46000
November 2015	7.77607	3.45600	3.26600	3.46000
December 2015	7.77607	3.45600	3.26600	3.46000

APPENDIX 9

Table 7 Rosuvastatin SEP comparison: January 2012 to December 2015

Month	Crestor 20mg	Zuvamor 20mg	Vusor 20mg	Storwin 20mg	Rosvator 20mg	Mediscor Reference Price
January 2012	8.241670					
February 2012	8.241670					
March 2012	8.418000					
April 2012	8.418000					
May 2012	8.418000					
June 2012	8.418000					
July 2012	8.418000					
August 2012	8.418000					
September 2012	8.418000					
October 2012	8.418000					
November 2012	8.418000					
December 2012	8.418000					

Month	Crestor 20mg	Zuvamor 20mg	Vusor 20mg	Storwin 20mg	Rosvator 20mg	Mediscor Reference Price
January 2013	8.418000	7.155360				
February 2013	8.418000	7.155360				
March 2013	8.906330	7.155360				
April 2013	8.906330	7.155360				7.160000
May 2013	8.906330	7.155360				7.160000
June 2013	8.906330	7.155360				7.160000
July 2013	8.906330	7.155360				7.160000
August 2013	8.906330	7.155360				7.160000
September 2013	8.906330	7.155360	5.343670	5.343670		7.160000
October 2013	8.906330	7.155360	5.343670	5.343670	7.125000	7.160000
November 2013	8.906330	7.155360	5.343670	5.343670	7.125000	7.160000
December 2013	8.906330	7.155360	5.343670	5.343670	7.125000	7.160000

Month	Crestor 20mg	Zuvamor 20mg	Vusor 20mg	Storwin 20mg	Rosvator 20mg	Mediscor Reference Price
January 2014	8.906330	7.155360	5.343670	5.343670	7.125000	5.350000
February 2014	8.906330	7.155360	5.343670	5.343670	7.125000	5.350000
March 2014	8.906330	7.155360	5.343670	5.343670	7.125000	5.350000
April 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
May 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
June 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
July 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
August 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
September 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
October 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
November 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
December 2014	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000

Month	Crestor 20mg	Zuvamor 20mg	Vusor 20mg	Storwin 20mg	Rosvator 20mg	Mediscor Reference Price
January 2015	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
February 2015	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
March 2015	9.424670	7.571790	5.654330	5.654670	5.654670	5.660000
April 2015	10.131330	8.139640	5.654330	5.654670	6.078670	5.660000
May 2015	10.131330	8.139640	6.075670	6.078670	6.078670	6.080000
June 2015	10.131330	8.139640	6.075670	6.078670	6.078670	6.080000
July 2015	10.131330	8.139640	6.075670	6.078670	6.078670	6.080000
August 2015	10.131330	8.139640	6.075670	6.078670	6.078670	6.080000
September 2015	10.131330	8.139640	6.075670	6.078670	6.078670	6.080000
October 2015	10.131330	8.139640	6.075670	6.078670	6.078670	6.080000
November 2015	10.131330	8.139640	6.075670	6.078670	6.078670	6.080000
December 2015	10.131330	8.139640	6.075670	6.078670	6.078670	6.080000

APPENDIX 10

Table 8 Candesartan utilisation, price and expenditure January 2012 to December 2015

Month	Total Beneficiaries	Total DDD Dispensed	DDD dispensed per 100 000 beneficiaries	Total Monthly Cost	Average Price per DDD	Reference Price Co-Pay	Total Monthly Expenditure	Average Expenditure per DDD
January 2012	465414	27973	6010.35	117091.84	4.19	0	117091.84	4.19
February 2012	465208	29734	6391.55	125627.39	4.23	0	125627.39	4.23
March 2012	463292	31278	6751.25	133093.88	4.26	0	133093.88	4.26
April 2012	468478	28466	6076.27	119671.52	4.20	0	119671.52	4.20
May 2012	460143	30264	6577.09	129342.41	4.27	0	129342.41	4.27
June 2012	460172	27744	6029.05	118015.65	4.25	0	118015.65	4.25
July 2012	461013	26938	5843.22	115115.04	4.27	0	115115.04	4.27
August 2012	460341	27864	6052.90	120239.86	4.32	0	120239.86	4.32
September 2012	460522	24837	5393.23	106663.60	4.29	0	106663.60	4.29
October 2012	460767	28125	6103.95	120953.97	4.30	0	120953.97	4.30
November 2012	460979	27168	5893.54	115546.97	4.25	0	115546.97	4.25
December 2012	461673	24817	5375.45	103335.72	4.16	0	103335.72	4.16

Month	Total Beneficiaries	Total DDD Dispensed	DDD dispensed per 100 000 beneficiaries	Total Monthly Cost	Average Price per DDD	Reference Price Co-Pay	Total Monthly Expenditure	Average Expenditure per DDD
January 2013	469039	26705	5693.56	112970.82	4.23	0	112970.82	4.23
February 2013	467804	26506	5666.05	112004.09	4.23	0	112004.09	4.23
March 2013	467846	26524	5669.39	116516.34	4.39	0	116516.34	4.39
April 2013	474404	25597	5395.61	114066.18	4.46	0	114066.18	4.46
May 2013	475467	29161	6133.13	128911.23	4.42	0	128911.23	4.42
June 2013	475451	25590	5382.26	112747.43	4.41	0	112747.43	4.41
July 2013	476790	26391	5535.14	117178.49	4.44	0	117178.49	4.44
August 2013	477527	27291	5715.07	119435.78	4.38	0	119435.78	4.38
September 2013	489698	26667	5445.60	117182.92	4.39	0	117182.92	4.39
October 2013	489979	29236	5966.79	127128.33	4.35	0	127128.33	4.35
November 2013	489561	27992	5717.78	121753.86	4.35	0	121753.86	4.35
December 2013	490125	25366	5175.41	108679.54	4.28	0	108679.54	4.28

Month	Total Beneficiaries	Total DDD Dispensed	DDD dispensed per 100 000 beneficiaries	Total Monthly Cost	Average Price per DDD	Reference Price Co-Pay	Total Monthly Expenditure	Average Expenditure per DDD
January 2014	495295	28243	5702.26	105908.11	3.75	0	105908.11	3.75
February 2014	493554	26832	5436.49	88918.50	3.31	37595.92	51322.58	1.91
March 2014	493226	28779	5834.85	91128.18	3.17	35786.78	55341.40	1.92
April 2014	491407	24813	5049.38	76484.00	3.08	29564.33	46919.67	1.89
May 2014	491249	25983	5289.17	78706.67	3.03	29430.66	49276.01	1.90
June 2014	491272	24540	4995.20	74051.09	3.02	27285.80	46765.29	1.91
July 2014	491457	25452	5178.89	78298.93	3.08	28743.99	49554.95	1.95
August 2014	491795	26063	5299.57	77757.37	2.98	27784.00	49973.37	1.92
September 2014	492033	23260	4727.33	68143.17	2.93	23107.50	45035.67	1.94
October 2014	492568	29994	6089.31	89675.23	2.99	32635.41	57039.81	1.90
November 2014	491848	25211	5125.77	76887.46	3.05	26885.59	50001.88	1.98
December 2014	492540	23590	4789.46	68958.40	2.92	23843.29	45115.10	1.91

Month	Total Beneficiaries	Total DDD Dispensed	DDD dispensed per 100 000 beneficiaries	Total Monthly Cost	Average Price per DDD	Reference Price Co-Pay	Total Monthly Expenditure	Average Expenditure per DDD
January 2015	501949	24870	4954.69	69127.24	2.78	21361.56	47765.68	1.92
February 2015	500695	26782	5348.96	75929.20	2.84	23459.97	52469.23	1.96
March 2015	500030	26709	5341.48	75491.91	2.83	24291.94	51199.97	1.92
April 2015	499210	25021	5012.12	70261.02	2.81	21437.59	48823.42	1.95
May 2015	500567	26356	5265.23	73729.35	2.80	23100.56	50628.79	1.92
June 2015	501548	24018	4788.77	67048.47	2.79	20424.01	46624.46	1.94
July 2015	502770	24916	4955.75	67415.16	2.71	19499.82	47915.35	1.92
August 2015	507329	24649	4858.58	69541.60	2.82	21627.67	47913.93	1.94
September 2015	502570	23061	4588.61	67736.21	2.94	21987.18	45749.03	1.98
October 2015	501964	23143	4610.49	68553.89	2.96	22355.42	46198.47	2.00
November 2015	502215	21756	4332.01	65668.18	3.02	23461.58	42206.60	1.94
December 2015	503486	21478	4265.86	67314.48	3.13	25240.02	42074.46	1.96

APPENDIX 11

Table 9 Candesartan utilisation, price and expenditure January 2012 to December 2015

Month	Total Beneficiaries	Total DDD Dispensed	DDD dispensed per 100 000 beneficiaries	Total Monthly Cost	Average Price per DDD	Reference Price Co-Pay	Total Monthly Expenditure	Average Expenditure per DDD
January 2012	465414	87115.50	18717.85	684170.23	7.85	0	684170.23	7.85
February 2012	465208	90365.50	19424.75	713375.66	7.89	0	713375.66	7.89
March 2012	463292	95586.00	20631.91	771135.44	8.07	0	771135.44	8.07
April 2012	468478	86729.50	18513.04	705261.33	8.13	0	705261.33	8.13
May 2012	460143	91737.50	19936.74	744520.94	8.12	0	744520.94	8.12
June 2012	460172	87396.50	18992.14	706724.53	8.09	0	706724.53	8.09
July 2012	461013	86300.00	18719.65	694588.72	8.05	0	694588.72	8.05
August 2012	460341	89669.50	19478.93	722196.26	8.05	0	722196.26	8.05
September 2012	460522	79482.00	17259.11	643069.16	8.09	0	643069.16	8.09
October 2012	460767	90787.50	19703.56	740948.95	8.16	0	740948.95	8.16
November 2012	460979	85835.50	18620.26	691204.82	8.05	0	691204.82	8.05
December 2012	461673	83412.00	18067.33	674901.01	8.09	0	674901.01	8.09

Month	Total Beneficiaries	Total DDD Dispensed	DDD dispensed per 100 000 beneficiaries	Total Monthly Cost	Average Price per DDD	Reference Price Co-Pay	Total Monthly Expenditure	Average Expenditure per DDD
January 2013	469039	94899.50	20232.75	760314.42	8.01	0	760314.42	8.01
February 2013	467804	94533.50	20207.93	759806.47	8.04	0	759806.47	8.04
March 2013	467846	94708.00	20243.41	773736.19	8.17	0	773736.19	8.17
April 2013	474404	96039.50	20244.24	788043.44	8.21	137066.18	650977.27	6.78
May 2013	475467	103173.50	21699.40	829620.29	8.04	137055.54	692564.74	6.71
June 2013	475451	88400.50	18592.98	698736.60	7.90	109376.95	589359.65	6.67
July 2013	476790	93748.50	19662.43	742237.03	7.92	163953.61	578283.42	6.17
August 2013	477527	100521.50	21050.43	790899.39	7.87	115474.07	675425.32	6.72
September 2013	489698	89913.00	18360.91	702092.79	7.81	97056.76	605036.03	6.73
October 2013	489979	94665.00	19320.22	726286.37	7.67	95281.21	631005.16	6.67
November 2013	489561	97391.00	19893.54	745261.02	7.65	97482.94	647778.08	6.65
December 2013	490125	90051.50	18373.17	687175.11	7.63	89060.29	598114.81	6.64

Month	Total Beneficiaries	Total DDD Dispensed	DDD dispensed per 100 000 beneficiaries	Total Monthly Cost	Average Price per DDD	Reference Price Co-Pay	Total Monthly Expenditure	Average Expenditure per DDD
January 2014	495295	113694.00	22954.80	802628.41	7.06	229286.80	573341.61	5.04
February 2014	493554	103632.50	20997.20	721795.59	6.96	201566.00	520229.60	5.02
March 2014	493226	113244.00	22959.86	777815.25	6.87	213896.03	563919.22	4.98
April 2014	491407	106326.50	21637.16	729561.85	6.86	197447.24	532114.61	5.00
May 2014	491249	108866.50	22161.16	748878.76	6.88	197592.52	551286.24	5.06
June 2014	491272	104519.50	21275.28	709807.96	6.79	185943.04	523864.92	5.01
July 2014	491457	106503.00	21670.87	725705.90	6.81	186840.97	538864.93	5.06
August 2014	491795	104463.50	21241.27	709341.14	6.79	175264.32	534076.83	5.11
September 2014	492033	97726.50	19861.78	654833.17	6.70	161092.84	493740.33	5.05
October 2014	492568	115080.50	23363.37	771601.36	6.70	190393.18	581208.18	5.05
November 2014	491848	100054.50	20342.57	674058.12	6.74	163895.37	510162.76	5.10
December 2014	492540	93712.50	19026.37	627892.22	6.70	150555.19	477337.03	5.09

Month	Total Beneficiaries	Total DDD Dispensed	DDD dispensed per 100 000 beneficiaries	Total Monthly Cost	Average Price per DDD	Reference Price Co-Pay	Total Monthly Expenditure	Average Expenditure per DDD
January 2015	501949	112902.00	22492.72	729548.28	6.46	157883.87	571664.41	5.06
February 2015	500695	117952.00	23557.65	758073.03	6.43	162712.43	595360.60	5.05
March 2015	500030	115480.00	23094.61	745705.07	6.46	158249.30	587455.76	5.09
April 2015	499210	113386.50	22713.19	711726.09	6.28	152492.58	559233.50	4.93
May 2015	500567	111730.50	22320.79	716819.23	6.42	145346.92	571472.31	5.11
June 2015	501548	103461.00	20628.33	660897.68	6.39	132690.66	528207.02	5.11
July 2015	502770	118827.00	23634.47	747644.50	6.29	149621.99	598022.51	5.03
August 2015	507329	110858.50	21851.40	701553.76	6.33	137585.18	563968.58	5.09
September 2015	502570	111752.00	22236.11	706080.62	6.32	139835.33	566245.29	5.07
October 2015	501964	107682.00	21452.14	679310.07	6.31	131744.85	547565.23	5.09
November 2015	502215	101675.50	20245.41	647618.68	6.37	125995.00	521623.68	5.13
December 2015	503486	97690.00	19402.72	619807.06	6.34	117920.23	501886.83	5.14