A Case Study on the impact of international benchmarking on the price of medicines in South Africa using immunosuppressive medicines for transplant recipients for comparison.

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DECLARATION

In fulfilment of the requirements of the coursework degree of Masters of Pharmacy in the Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa, I, Kerry-Louise Cassar, declare as follows:

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ACRONYMS AND TERMS

AEMP	Approved ex-manufacturer price
AC	Autonomous communities
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BRICS	Brazil Russia India China South Africa
CADTH	Canadian Agency for Drugs and Technologies in Health
EDL	Essential Drug List
EMA	European Medicines Agency
ERP	External reference pricing
FDA	Food and Drug Administration
Gazette methodology	Government Gazette 37625 Regulations relating to a transparent pricing system for medicines and scheduled substances (benchmark methodology) 2014
IBM	International Benchmarking of Medicines
INN	International Non-proprietary Name
IVA	Impuestos sobre el Valor Añadido (VAT)
MSSSI	Ministerio de Sanidad, Servicios Sociales e Igualdad (Ministry of Health, Social Services and Equality)
MSPS	Ministry of Health and Social Policy (Spain)
NHI	National Health Insurance
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PBS	Pharmaceutical Benefits Scheme (Australia)
PBPA	Pharmaceutical Benefits Pricing Authority (Australia)
PE	Pharmacoeconomic evaluations
PHARMAC	The Pharmaceutical Management Agency (New Zealand)
PMPRB	Patented Medicines Prices Review Board
PTAC	Pharmacology and Therapeutics Advisory Committee (New Zealand)
PVL	Precio industrial maximo de los medicamento
PVP	Precio de venta al público
RCMP	Royal Canadian Mounted Police

SEP	Single Exit Price
SNS	Spanish National Health Service
TGA	Therapeutic Goods Administration (Australia)
VAT	Value Added Tax

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CHAPTER 1

1.1 Introduction

According to the Council for Medical Schemes' Annual report 2017/2018, 16.08% of total benefits paid by medical schemes in 2017 were for medicines [1]. This high percentage of spend on medicines in the medical aid population in South Africa highlights the importance of medicine price regulation and the need for robust tools and policies to contain costs. Examples of regulatory instruments used globally include, but are not limited to, internal reference pricing of genericised molecules; external reference pricing (ERP) or international reference pricing (IRP); price freezes; price cuts; price volume agreements; inflation rate price increases and pharmacoeconomic evaluations [2]. In 2005, the South African Minister of Health published a government gazette of regulations relating to a transparent pricing system for medicines and scheduled substances [3]. The Single Exit Price (SEP) legislation detailed in this gazette aimed to regulate medicine pricing and remove the practice of discounts and rebates where benefits were not reaped by consumers [2]. Initially when implemented, the SEP had a significant impact on the price of medicines and medicine expenditure but over time a rebound in pricing was observed [2]. However, the SEP implementation was only intended to be the first phase of addressing medicine price concerns at the ex-manufacturer level [2]. To address the second phase, it was noted in 2005 Gazette that the Minister must publish in the Gazette, a methodology for conforming to international benchmarks. In December 2006 the initial methodology for international benchmarking of the prices of medicines and scheduled substances in South Africa was published for comment [4]. In December 2010, a subsequent detailed proposed methodology addressing commentary was published for further comment [2]. In May 2014, the most recent proposed methodology for regulations relating to a transparent pricing system for medicines and scheduled substances (benchmark methodology) was published [5].

"The *aim* of international benchmarking, together with other regulatory interventions, is to: *Protect the South African health system from paying distorted prices for medicines through the elimination of price distortions and price distorting behaviour."* [2]. The Pricing Committee and the National Department of Health wish to establish a programme in South Africa that involves negotiating drug prices that relate to their therapeutic performance but also takes in to account socioeconomic factors [5]. The proposed methodology for international benchmarking of medicines (IBM), referred to internationally as external reference pricing (ERP), requires that the lowest price in a selected basket of countries be used as the ultimate price for the purposes of benchmarking. The selected basket of countries includes Australia, Canada, New Zealand, Spain and South Africa [5]. The Department of Health may review the basket every two years and a possible complementary list of benchmark countries may be published online [5].

In addition to the application of the single exit price (SEP) of a medicine, further medicine pricing tools exist to promote generic utilisation and medicine cost reduction. Internal reference price systems encourage prescribers and patients to use less costly generically similar medicines, and stimulate market pricing shifts. However, in the case of immunosuppressive medicines in transplant recipients, the implementation of generic reference pricing systems is challenged by the concerns associated with generic switching in these patients [6]. The South African Renal Society issued a consensus statement stipulating that there is insufficient scientific evidence to conclude that use of generic immunosuppressants in solid organ transplants is safe, and should generic use be imposed by funders in this setting, the society has listed precautions that should be taken to mitigate the risk of organ rejection [6]. Allard et al conducted a literature review to determine the ethical acceptability of prescribing generic immunosuppressive drugs to renal transplant patients [7]. The authors concluded that it would be ethical to prescribe generic immunosuppressive drugs provided certain conditions were met [7]. These included regulatory safeguards to minimize the risks of substitution; education of patients; and further studies to ascertain the risks and costs related to the substitution of immunosuppressive drugs [7]. Highlighting the controversial nature of the topic, the authors included position statements on the use of generic immunosuppressive drugs from the Canadian Society of Transplantation, the American Society of Transplantation, and the European Society of Organ Transplantation [7]. Overall, the main concern surrounds uncontrolled substitutions of different generics due to the theoretical possibility of 'generic drift', where a generic at one end of the area under the curve (AUC) may not be bioequivalent to a generic at the other end of the acceptable AUC range [7].

With the concerns of unsupervised generic substitution of immunosuppressive medicines in transplant patients limiting the use of internal generic reference pricing tools to drive down the cost of medicines in this therapeutic area, the use of international benchmarking of medicine prices poses another potential strategy for medicine price regulation.

1.2 Background

In a review of pricing and reimbursement policies on the affordable access to medicines in European Union (EU) countries, it was noted that only two EU member states, Sweden and the United Kingdom, do not apply a form of external reference pricing [8]. However, despite the widespread implementation of EPR in various forms, there is still limited literature on the impact of EPR on affordable access to medicines [8]. Some evidence suggests that in countries applying EPR to new patented medicines, the national list prices were lower than in countries not applying EPR [8].

With the aim of including benchmark countries with an effective system for regulating and pricing medicines, the four countries, Australia; New Zealand; Canada and Spain, met the following criteria for selection by [2]:

1. Having regulatory authorities that licence and ensure the quality of medicines;
2. Having systems in place for the effective regulation of medicine prices, particularly through powerful purchasing structures;
3. Having accessible, structured pricing information that is regularly updated and reflective of the actual prices at which medicines are sold; and
4. Having implemented internationally accepted rules on patent and intellectual property rights protection.

1.2.1 Health system overviews

This section will outline the health systems of the basket countries as well as those of South Africa.

1.2.1.1 South Africa

The South African health system is currently two tiered with a relatively small percentage of South Africans belonging to a medical insurance scheme, 17.4% in 2016 [9]. Some South Africans may access private healthcare services by self-payment, however the majority of uninsured South Africans access healthcare via state sector services. The government has been working towards the implementation of a National Health Insurance system to provide equitable care for all.

The draft National Health Insurance Bill was published for comment on the 21st June 2018 [10] and "The objective of the Act is to establish a Fund that aims to achieve sustainable and affordable universal access to health care services by

a) establishing and maintaining an efficient Fund through the consolidation of revenue so as to protect users against financial risk;
b) serving as the single public purchaser of health services in terms of this Act so as to ensure the equitable and fair distribution and use of health care services;
c) ensuring sustainability of funding for health care services;
d) and providing for equity and efficiency in funding by actively purchasing health care services, medicines, health goods and health related products from certified, accredited and contracted service providers."

"The aim of the National Health Insurance (NHI) is to provide access to quality and affordable healthcare services for all South Africans based on their health needs, irrespective of their socio-economic status" [9]. In order to achieve these, there are two regulatory authorities outlined in the Act to carry out specific functions. South African Health Products Regulatory Authority (SAHPRA)

governs registration of medicines for South Africa applying the Medicines and Relates Substances Act in its mandate [11]. Applying the same Act, the National Medicines Pricing Committee is responsible for transparent pricing of registered medicines. Medicine in the private sector is subject to the SEP legislation, Dispensing Fee regulations and voluntary pharmacoeconomic guidelines and product and medicine pricing information is available on the South African Medicine Price Registry [12]. In the state sector, medicines are obtained via competitive tender processes and are not subject to SEP legislation [13].

1.2.1.2 Canada

The Canada Health Act aims "to protect, promote and restore the physical and mental well-being of residents of Canada and to facilitate the reasonable access to health services without financial or other barriers" [14]. The intention is to ensure that eligible residents have access to insured health services without direct payment charges at the service points [14]. Prescription drug therapy administered in-hospital is publicly funded under the Canada Health Act. However, outpatient prescriptions are excluded from coverage but may be covered by private insurance plans and programmes run by the federal, provincial and territorial governments [14]. Provincial and territorial governments may provide publicly funded drug programmes for eligible populations like senior citizens or for diseases associated with high drug costs [14]. The Government of Canada provides prescription drug coverage for members of eligible groups including First Nations and Inuit, members of the military, Veterans, Royal Canadian Mounted Police (RCMP) members and inmates of federal penitentiaries [14].

Health Canada is responsible for approving a drug for use in Canada; the Canadian Agency for Drugs and Technologies in Health (CADTH) provides reimbursement recommendations to public drug plans [15] and the Patented Medicines Prices Review Board (PMPRB) regulates the price of patented medicines in Canada [16]. With the exception of Quebec, the CADTH Common Drug Review (CDR) process was introduced in 2003 to replace the independent review conducted in 18 jurisdictions in Canada [15]. CADTH uses the CDR process to provide reimbursement recommendations to Canada's federal, provincial and territorial public drug plans [15]. CADTH will only issue a recommendation once a drug has been approved for use by Health Canada [15].

1.2.1.3 Spain

Health system reviews of Spain as a health care system in transition provide a broad insight into the country's health system [17, 18]. The Health Care General Act of 1986 set the groundwork for a reform from a social security system to a national health service known as the Spanish National Health Service (SNS). The SNS is defined as 'all structures and public services at the service of health' and 'the combination of state administration and autonomous communities (AC) health services'. The general

principles of the SNS include: Universal coverage with free access to health care for all citizens; Public financing mainly through taxation; Integration of health service networks; Political devolution of health services to autonomous communities (ACs) and region-based organization; A model of primary healthcare emphasizing integration of promotion, prevention and rehabilitation activities in health care zones [17]. As per the administration of the country, the health system is managed both regionally by the 17 Autonomous Communities, with national strategic oversight; health system coordination and performance monitoring [18]. With the national Ministry of Health responsible for drug approval and pricing and the regional ACs responsible for the pharmaceutical expenditure, tension has been observed with the implementation of various reimbursement policies [18].

The Ministry of Health, Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI), is responsible for coordinating the SNS, drafting health policies and legislation [18]. The Spanish Agency of Medicines functions as the regulatory authority for the registration of products, in addition to the broader European regulation performed by the European Medicines Agency (EMA) [18]. The National Commission for the Rational Use of Pharmaceuticals comprises representatives from various stakeholders and is responsible for reimbursement decisions. The General Directorate of Pharmacy and Health Products ascertains which products should be subsidised by the public budget by means of negative lists. A generic reference pricing system has been in place since 2003 and a consequence of this system has been a decrease in medicine prices. The Directorate also set the guidelines for the Drug-Policies Commission to follow when making a drug pricing decision. The Inter-Ministerial Commission on Prices of Medicines is responsible for deciding drug prices after reviewing the submission of the manufacturers [17].

The Act for Guarantees and Rational Use of Pharmaceuticals and Health Products regulates various aspects of the chain of supply of drugs and medical products including clinical research, registration, regulation for rational use, public funding among other aspects. The regulation enforces negative lists which exclude drugs deemed to be of low or no therapeutic value [17]. In 2011 the regulations enforced the prohibition of brand name prescription, further strengthening the reference pricing system already in place [18].

Three publicly funded mutual funds are the exception to the National Health Service and are offered to civil servants forming a quasi-public service. Civil servants are the only citizens who have the option of fully private healthcare. Until 2012, in-hospital pharmaceutical services were fully reimbursed, however outpatients services were subject to a co-payment. Pensioners and their beneficiaries were exempt from a co-payment and certain groups may have been be subject to a reduced co-payment, including AIDS patients and chronic disease patients [17]. In 2012, new regulation categorised the SNS

offering into three different benefit packages: "(a) the basic package for all those insured and their dependents, which includes "essential" activities, including medical visits and hospitalisations; (b) a "supplementary" package, cost-shared by the patients, including pharmaceutical benefits (in practice, co-payment affects mainly outpatient pharmaceutical prescriptions and specific orthesis and orthopaedic prosthesis); and, (c) an "accessory" package, which includes "non-essential" activities, still vaguely defined."[18]. The regulation reform in 2012 also saw changes to the cost-sharing system. The common basic package is exempt from cost-sharing, however cost-sharing applies to outpatient drug prescriptions in the supplementary and accessory package. The level of co-payment is determined by household income and pensioners are no longer excluded, however a monthly cap is applied. Medicines prescribed and dispensed in retail pharmacies for AIDS patients and most chronic medicines are subject to a 10% co-payment and a per prescription cap [18].

1.2.1.4 New Zealand

The fundamental aspect of New Zealand's comprehensive health system is that it is built on the approach that everyone gets "a fair go" in life [19]. The New Zealand Public Health and Disability Act of 2000 establishes the framework for public sector funding, the organization, the strategic direction and goals for healthcare and disability services. The Health Act of 1956 clarifies the roles and responsibilities of the individuals responsible, and the Crown Entities Act of 2004 establishes the statutory framework for the establishment, governance and operations of the Crown entities [20] which are bodies established by law in which the Government has controlling interest [21]. New Zealand has established a Health Strategy for Future Direction for the years 2016 to 2026 with five themes – people-powered, closer to home, value and high performance, one team and smart system – to guide the path to the future they envision as a country [20].

Overall, general taxation provides the main form of funding for New Zealand's health system and this involves funding from government in the form of Vote Health, the Accident Compensation Corporation (ACC), other government agencies and local government. Private funding in the form of insurance and out-of-pocket payments also contribute to the system's funding [20].

Medsafe is the New Zealand Medicines and Medical Devices Safety Authority and is responsible for the regulation of medicines and medical devices in New Zealand ensuring they are acceptably safe [22]. Medsafe's mission is to enhance the health of New Zealanders by regulating medicines and medical devices to maximise safety and benefit [22].

The New Zealand government's strategy for the medicines system is known as Medicines New Zealand and encompasses the outcomes of access, including equitable access, optimal use and quality of

medicines. Where quality of medicines would form part of the realm of function of Medsafe, Pharmac is responsible for the optimal use of and access to medicines in New Zealand. Pharmac aims to provide the best health outcomes within the available financial budget [23]. Ultimately, Pharmac decided which medicines and medical devices are funded by the government and this includes community, cancer, hospital medicines, vaccines and medical devices.

The Pharmacology and Therapeutics Advisory Committee (PTAC) was established under the Public Health and Disability Act of 2000. Its role is to provide Pharmac with objective clinical advice in order to make reimbursement decisions. PTAC holds four annual meetings and Pharmac must submit requests for advice on funding applications before the scheduled deadlines. The committee comprises a wide range of senior health practitioners who are appointed by the Director-General of Health [23].

1.2.1.5 Australia

Through government funding via a Medicare levy, Australia provides universal access to healthcare by subsidizing free access to services in state hospitals and out-of-hospital medical treatment, for example doctors; specialists; optometrists and allied health professionals [24]. Private medical insurance for private hospital treatment is available and in 2014, almost half of the Australian population had private medical cover [25]. The Medicare Benefits Schedule operates under the legislative auspices of the Health Insurance Act 1973 and the National Health Act 1952 [26].

The Australian National Medicines Policy focusses on access to and the wise use of medicines [27]. Initiated in 1985 with the WHO Revised Drug Strategy, a National Medicines Policy was developed and implemented over many years, resulting in the publication of a revised policy in 1999 [27]. The policy is based on partnerships with awareness of social and economic policy and states “Cost should not constitute a substantial barrier to people’s access to medicines they need, therefore, normal market mechanisms may be tempered in access arrangements, to increase the affordability of important medicines” [27]. It takes in to account people’s needs and integrates the skills, experience and knowledge of the partners with an emphasis on health outcomes rather than programme inputs [27]. The four central objectives are: Timely access to the medicines that Australians need, at a cost that individuals and the community can afford; Medicines meeting appropriate standards of quality, safety and efficacy; Quality use of medicines; and Maintaining a responsible and viable medicines industry [27].

The Therapeutic Goods Administration (TGA) forms part of the Australian Government Department of Health and is the regulatory body for medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products [28]. The goods are assessed for safety and efficacy for inclusion in

the Australian Register of Therapeutic Goods (ARTG) [25]. In order to be made available in Australia, goods must be listed on the ARTG. Therefore, a pharmaceutical product can't be listed on the Pharmaceutical Benefits Schedule (PBS) if not registered by the TGA [25].

The Pharmaceutical Benefits Scheme (PBS) provides government subsidised medicine to Australians. It was initially developed in 1948 as an essential medicines list for pensioners, and a "life-saving and disease preventing" list for all. The objective of the PBS today is to provide "timely, reliable and affordable access to necessary medicines" [29]. Out-of-hospital prescriptions are subject to a maximum co-payment amount per prescription and a concessional co-payment rate applies to pensioners and low-income earners [25]. Once a family/individual has reached the safety net spend in a calendar year, the concessional co-payment rate applies, and once a pensioner or low-income earner has reached their pre-specified safety net, no co-payment applies [25].

The Australian Government appoints an independent expert body to recommend new medicines for listing on the Pharmaceutical Benefit Scheme. The committee is known as the Pharmaceutical Benefits Advisory Committee (PBAC) and is made up of experts including doctors, health professionals, health economists and consumer representatives. The Drug Utilisation Sub Committee and the Economics Sub Committee assist with the analysis of the clinical effectiveness, safety and cost effectiveness of a new medicine compared to other available treatment for the same condition [29].

1.2.1.6 BRICS

Brazil, China, Russia, India and South Africa are five leading emerging economies whose leaders convene annually at the BRICS Leaders' Summit [30]. The aim of the cooperation among the countries is non-competitive, sustainable, equitable and mutually beneficial development [30]. South Africa joined the BRIC Member States in April 2011 at the Third BRICS Summit, a recognition of the role the country plays in the socio-economic regeneration of the African Continent [30].

The countries engage on healthcare with health ministers meeting annually, and as emerging economies, tackle key common health issues. At their initial meeting, the health ministers discussed four priorities: "strengthening their health systems, primarily by developing and ensuring access to health technologies, the double burden of infectious and noncommunicable diseases, support for international organizations, such as WHO and UNAIDS as well as global health partnerships, and promoting technology transfer to developing countries" [31]. At the Health Ministers BRICS Meeting in South Africa in July 2018, the five key issues discussed were tuberculosis, noncommunicable diseases, universal health coverage, access to medicines and vaccines and the implementation of International Health Regulations 2005 [30].

1.2.2 Medicine pricing approaches of Canada, Spain, Australia and New Zealand

1.2.2.1 Canada

Pricing of off-patent original products and generic products are not directly regulated in Canada [2]. The Patented Medicine Prices Review Board (PMPRB) was formed as a result of the Patent Act of 1987 [16]. In accordance with the Patent Act and the Patented Medicines Regulations, patentees must file pricing information at introduction and then twice a year until the patent expires [32]. The PMPRB reviews the average price of each strength of an individual dosage for the purpose of establishing the Maximum Average Potential Price at introduction for the new patented product; and assessing whether the price of an existing patented drug is excessively priced. For the latter the board takes the following five factors into account as detailed in section 85 of the Patent Act [32]: the prices at which the medicine has been sold in the relevant market; the prices at which other medicines in the same therapeutic class have been sold in the relevant market; the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States); changes in the Consumer Price Index; any other factors that may be set out in regulations.

The PMPRB may order remedial action be taken where excessive pricing of patented medicine is determined. Depending on the status of the patented medicine, the board may order that a patentee or former patentee reduce the price at which the patentee sells the medicine in any market in Canada; reduce the price at which the patentee sells one other patented medicine in any market in Canada; or make a payment to Her Majesty in right of Canada [32].

The Human Drug Advisory Panel (HDAP) provides expertise services to the PMPRB and will recommend the level of therapeutic involvement (breakthrough, substantial improvement, moderate improvement, slight or no improvement) of a drug product relative to other drug products sold in Canada [32]. A product is deemed to be excessive in price if the National Average Transaction Price or any Market-Specific Average Transaction Price exceeds the Maximum Average Potential Price at introduction, and this is determined by the pricing tests associated with the level of therapeutic involvement [16].

1.2.2.2 Spain

In Spain, only the manufacturer pricing of reimbursable prescription medication is regulated [2]. Price regulation for novel products is based on a profit cap approach where the price is set on the basis of a profit of 12%-18% of invested capital. A 20% reduction in price can be enforced on a medicine if a

product has a generic available, at a lower price in another EU country, but not in Spain [17]. A reference pricing system also applies when generics are available. The average price of the three lowest generics forms the reference price when a product has been on the local market for ten years and generics are locally available [2]. If a product is registered for a second indication, then the period on the market before the reference pricing applies is eleven years not ten [2].

1.2.2.3 New Zealand

Once Medsafe has approved a product for use in New Zealand, suppliers may set the price irrespective of whether the product is patented, a generic, an over-the counter (OTC) or prescription medication [2]. However, if the supplier wishes to obtain listing on the Pharmaceutical Schedule for reimbursement, then PHARMAC's coverage and reimbursement policies guide the pricing discussions [2]. These strategies include negotiation, tendering, Alternative Commercial Proposals (ACPs), Requests For Proposals (RFP), reference pricing (internal), rebates, expenditure caps and multi-product agreements [33].

1.2.2.4 Australia

The Pharmaceutical Benefits Pricing Authority (PBPA) applies different pricing methods in setting the prices of products listed on the PBS [2]. These include benchmark pricing, the cost plus method and the average monthly treatment cost [2]. The benchmarking method is the most common approach for products listed on the PBS [2]. A benchmark product is selected based on the lowest price and other products will be priced accordingly [2]. For new product listings, PBAC advises on specific relativities between drugs and the PBPA will apply this to the pricing decision [2]. Products for the non-PBS market have their price set by the manufacturer and are not subject to negotiation by PBAC [34].

1.3 Problem statement (Research problem)

Evidence regarding the impact of different pricing policies on medicine prices, especially in low income countries, is scarce. This issue is twofold as it refers not only to a lack of evidence but also a potential lack of successful pricing policy implementation [35, 36]. As detailed in the Gazette, the methodology for IBM proposes that the lowest price in a selected basket of reference countries be used as the local ex-manufacturer price. The selected basket of countries includes Australia, Canada, New Zealand, Spain and South Africa [5]. Literature assessing whether medicine prices would be lowered on implementation of this policy are lacking.

Furthermore, the current proposed basket of countries were selected on the basis of pre-specified criteria selecting countries with effective systems for pricing and regulating medicines [2]. However their health system structure and socio-economic background may be considered significantly different from

that of South Africa. As emerging economies, BRICS countries may pose as more suitable economic comparators, however literature on the use of BRICS countries as external reference pricing countries is lacking.

The South African state sector is currently not subject to the SEP legislation and makes use of tender processes to procure medicines by means of volume-based purchasing. A secondary analysis aims to provide insight into whether state tender prices remain consistently low when compared to private sector South African medicine prices and the Gazette benchmarking countries.

1.4 Objectives

The purpose of this observational analysis was to determine whether the implementation of the proposed methodology for IBM would have a positive (cost saving) impact on the prices of immunosuppressive medicines for transplant patients.

1.4.1 The primary comparison aims to assess the whether the application of IBM with the Gazette benchmark countries would lower the price of medicines locally.

1.4.2 The secondary analysis aims to assess whether using BRICS countries as a benchmark would lower the local price of medicine.

1.4.3 Furthermore, a comparison of the South African government sector tender prices with the five Gazette benchmark countries (South Africa private sector, Australia, Canada, New Zealand, Spain) aims to assess whether state tender prices are the lowest.

1.5 Significance of the study

The use of generic immunosuppressive medicines in maintenance immunosuppression is a controversial topic. There is a consensus among transplant societies that because immunosuppressive medicines are "critical dose drugs", health care providers should exercise caution when using generic immunosuppressive drugs [7].

Therefore, internal reference pricing as a cost minimisation tool may not be considered a feasible cost saving tool to implement for this particular group of medicines. If international benchmarking demonstrates a positive effect (would decrease the local price) on the medicine, then this may provide an alternative mechanism to lower the cost of medicines in this group in a manner that does not directly involve the person using the medicine.

Overall this study aims to provide a broad observational basis for the use of IBM and the proposed countries as a pricing tool, the feasibility of using BRICS countries as comparator countries, and then assess the local state tender pricing in relation to the IBM gazette benchmarking pricing.

1.6 Research questions

1.6.1 Would benchmarking against the four countries listed in the Gazette (Australia, New Zealand, Canada and Spain) decrease the South African medicine price?

1.6.2 Is the full benchmarking basket available (Australia, New Zealand, Canada and Spain)?

1.6.3 Which benchmarking country has the lowest price?

1.6.4 Would benchmarking against the remaining BRICS countries decrease the South African medicine price?

1.6.5 Is the state tender pricing lower than all Gazette benchmark countries.

1.7 Hypothesis

H_1 The application of international benchmarking reduces the price of immunosuppressive medicines

H_0 The application of international benchmarking does not reduce the price of immunosuppressive medicines.

CHAPTER 2

2.1 Literature review

2.1.1 Pricing policies

Medicine prices are controlled at various points in the distribution process, including ex-manufacturer or ex-factory level, ex-importer level, wholesaler level and at pharmacy level [37]. Medicine prices at these levels may be controlled by a variety of methods including cost-plus systems, profit ceilings, comparative pricing systems, price negotiation models and pharmacoeconomic evaluations [37]. The purpose of this research is to determine the impact of IBM or ERP on the cost of medicines at ex-manufacturer or ex-factory level.

2.1.2 Cost-plus systems

This pricing strategy involves determining a justifiable price level for a medicine, taking into account the research and development costs of the drug plus an acceptable profit margin. This would require transparent information from the manufacturing company, which itself could prove challenging, and it may result in a price that proves inflexible over time [37]. The 2015 WHO guidelines on country pricing recommend that countries should not use cost-plus pricing as an overall pharmaceutical pricing policy [38]. Based on the limitations in implementation of this model, it does not appear to be widely implemented. Medicine prices in Egypt are regulated by the government at all levels. Until 2012, the cost-plus method was implemented to set retail medicine prices requiring that manufacturers submit cost sheets for first to market medicines [39]. The implementation of decree #499 in June 2012 replaced the cost-plus method with external reference pricing for innovator products and a percentage markdown off the originator product price for generics [39]. The decree accommodated for price increase applications to be submitted on the basis of a product's cost sheet. When the decree was implemented, the government stipulated which medicines needed to undergo a price change in line with the decree. A descriptive pre-post observational study attempted to assess the short term impact on pricing and affordability of products that underwent a price change in the two waves of implementation in October 2012 and January 2013. The analysis suggested that higher priced imported branded products tended to decrease in price yet still remained unaffordable. Whereas products that increased in price tended to be lower priced locally manufactured generics and affordability was not negatively affected [39].

The United Kingdom Pharmaceutical Price Regulation Scheme allows the government to refuse a price increase application for existing medicines and can also demand price reductions for purchases by the National Health Service (NHS) [40]. Another example of a cost-plus pricing strategy is the mandatory price reduction implemented in Australia in 2005 which saw a once off 12.5% mandatory price reduction on the benchmark price. This was implemented once off to the first generic brand of a Pharmaceutical Benefit Schedule (PBS) listed medicine and the intention was for this to "flow-on" to different brands, strengths and formulations [41].

2.1.3 Profit ceilings

This method involves setting a cap on the profit that a company can make, not just a specific product [37]. In an article by Danzon and Kim, the authors recommend that a manufacturer's full portfolio of products, including-life-cycle price profiles, is taken in to account, as a portfolio of products shares joint costs [42]. Once again, this method may be hampered by a lack of transparency in research and development and manufacturing costs. The National Development and Reform Commission (NDRC) in China removed the use of price ceilings in June 2015 when evidence emerged that it was ineffective. However, the evidence of the impact may be confounded by other policies like a 15% mark-up rule in China that allowed prescribers and hospitals to add a mark-up on prescription medicines [43].

2.1.4 Pharmacoeconomic evaluations

Ultimately, pharmacoeconomic evaluations [PE] are a calculation of "how much the drug is worth to the community" in question [37]. These are complicated calculations that involve not only direct medicine costs, but also indirect costs, for example, loss of income due to disease. This model is used as an adjunctive tool in some countries and requires an expert group of people to perform such analyses [37]. Although pharmacoeconomic evaluations are an established component of medicine reimbursement policies in many developed countries, its implementation in many countries is still emerging. In December 2011, the Macedonian Agency of Medicines introduced international reference pricing for the establishment of wholesale and retail medicine prices. Pharmacoeconomic evaluation was introduced in parallel to international reference pricing. An observational analysis assessed the effects of the price changes and subsequent effects on sale volumes of the medicines affected. The authors did not observe a clearly defined pattern of sequelae from the implementation of the reference pricing for future policy guideline inclusion, and therefore noted that pharmacoeconomic studies have to be implemented as a component of global pricing strategies [44].

The use of Health Technology Assessment (HTA) and cost effectiveness research (CER) are new in China and guidelines for the use of HTA are being developed but have yet to be included in broader national policy. In Zhejiang province, a pharmacoeconomic committee has been established to assist in the tender pricing process [43].

The use of pharmacoeconomic evaluations was considered in the selection of the proposed basket of South African IBM comparator countries of Australia, New Zealand, Canada and Spain [2]. The respective organisations or committees involved in the pharmacoeconomic evaluations include the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia advising the PBS, the Pharmacology and Therapeutics Advisory Committee (PTAC) advising Pharmac in New Zealand and the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada [29, 33, 15].

Pharmacoeconomic evaluations seem to be used in a less formal extent in Spain [2], and despite the creation of formal HTA networks, it is not clear that pharmacoeconomic evaluations are included in these networks [17]. In South Africa, pharmacoeconomic submission by manufacturers as part of their local registration application is on a voluntary basis [12].

2.1.5 Price negotiation models

It would be impractical to expect a negotiation between a single patient and a pharmaceutical manufacturer to lead to a price reduction for the patient [37]. Buying power is a critical factor in negotiation and the more volume consumption the buyer has to offer, the more negotiation power is generated. In South Africa, the state health sector has the greatest bargaining power as it serves the largest proportion of patients and operates by means of a state tender process for medicines. Medicine prices are often significantly lower for items purchased on state tender than in the private sector where buying power is smaller and negotiation of prices is not permitted [12, 13]. Both the New Zealand Pharmac schedule and the Department of Veteran Affairs in the US make use of competitive tendering processes to set prices [45]. Botswana and Mozambique have a small percentage of the anti-tuberculosis medicine market relative to South Africa's potential purchasing volumes (South Africa holds more than 50% market share for anti-TB drugs in SADC-South African Development Community), yet they managed to secure lower prices for their anti-TB drugs [36]. This is an example of where volume bargaining power was not realised where it may have brought about savings.

In China, tendering has been the primary mechanism for medicine price containment. It is conducted at provincial level and has shown to reduce Essential Drug List (EDL) drug prices by 25% on average [43]. Secondary negotiation occurs at hospital level where the majority of medications are purchased in China. The volume-based negotiation may result in a price lower than the awarded tender price but it is unclear as to where the savings generated from this negotiation should be awarded. Due to regulatory capacity concerns, the quality of medicines in China, especially generics is a concern [43]. Up until 2015, generics could be registered on the basis of bioequivalence testing against other generics not against the originator product, leading to a lack of trust in generic quality and a large market for expensive off-patent originators. As part of tender reform, quality assessment and transparency in tender awards and secondary negotiation prices is a priority [43].

2.1.6 Comparative pricing

Comparative pricing policies observed in the literature include internal and external or international reference pricing. In order to set prices, the relevant pricing regulators of a particular country employing international benchmarking methods would compare prices with a set reference "basket" of countries. The regulator may choose to benchmark the price at the lowest or the average price [40]. This may be applied to new medicines or currently registered medicines [37]. In their WHO/HAI Working Paper

on ERP, Espin et al conclude that "Most of the alleged effects of ERP are not supported by any rigorous evaluative research that demonstrates whether this apparently easy-to-apply system is effective in setting a fair, efficient and sustainable price structure" [46]. In a review of pricing and reimbursement policies on the affordable access to medicines in European Union (EU) countries in 2017, it was noted that only two EU member states, Sweden and the United Kingdom, do not apply a form of external reference pricing [8]. Leopold et al conducted a descriptive overview of ERP in Europe in 2010 and the results showed that 24 of the 28 European countries surveyed employed ERP [47]. Most of these countries had fewer than 10 countries in their reference basket, used an average of the reference prices and applied ERP mainly for patented products. The authors could not identify an ERP best practice model as national policy frameworks differ among countries, but highlighted that price revisions and the informal exchange of pricing information should be conducted regularly [47]. It is also important to define the unit of comparison and rules for an approach when comparator pricing data is unavailable, for example, using internal reference pricing to provide ATC 5 or ATC 4 level pricing for the comparator country [47]. Leopold et al concluded that "ERP is a dynamic policy tool which is adjusted by policy makers over time"[47]. In another investigation by Leopold et al, the authors assessed the impact of ERP on medicine prices by conducting a comparison among 14 European countries [48]. The study concluded that prices of patented products were generally lower in countries applying ERP. The ex-factory price was used for the comparison because the majority of countries that use ERP use the ex-factory price which is devoid of mark-ups and VAT.

The Netherlands implemented international benchmarking in 1996, the maximum permissible price is based on the average wholesale price of the similar products in a basket of countries including Belgium, Germany, UK and France [37]. It brought about an average 20% decrease in the price of pharmaceuticals [37]. It may be challenging to choose a basket of benchmark countries as it would be preferable to choose countries of similar economic development, but this may be limiting if the similar countries do not have established price setting policies [40]. The proposed methodology for IBM (international benchmarking) in South Africa is that the lowest price in a selected basket of countries should be used as the ultimate price for the purposes of benchmarking. The selected basket of countries includes Australia, Canada, New Zealand, Spain and South Africa [5].

In 2011, Macedonia introduced a new methodology for the pricing of medicines in order to establish transparency, reduce medicine prices but maintain quality and stabilise supply. Wholesale and retail prices are established by comparing wholesale costs in reference countries including Slovenia, Bulgaria, the Netherlands, Poland, the United Kingdom, France, Croatia, Serbia, Greece, Germany, Turkey and the Russian Federation. Twice a year the highest wholesale prices for innovator and generic categories are published for each INN form, strength and packaging based on the average wholesale price in the reference countries. Zareski et al reviewed the effects of the implementation of the policy after four

years and acknowledged that the policy has brought about transparency and a decrease in price of more than 1500 generics and almost all originators. However the authors observed that pharmaceutical companies may have shifted their sales to different dosage forms of the same generic not affected by a price decrease. Manufacturers and importers may have decided to withdraw products where the reference pricing made it financially unreasonable to sell the product or where it may have then been referenced price by other countries resulting in a negative effect of the sales in other countries. In the time that the authors worked on the article they did not see any amendments to the list of reimbursed drugs which highlights that although prices of medicines may be decreased, this must not be done in isolation and reviews of essential medicines lists are required to ensure that access to the most cost effective medicines are provided [44].

Decree #499 in Egypt in October 2012 stipulated that the domestic retail price of an innovator product would be benchmarked in accordance to the lowest retail price worldwide for the exact same product. The ex-factory and wholesaler prices would also be set relative to the benchmarked retail price [39]. An observational analysis suggested that higher priced imported branded products tended to decrease in price yet still remained unaffordable.

China's pharmaceutical system is complex and is currently undergoing significant reform to improve transparency, decrease corruption and improve access to quality medicines [43]. In 2009, 42.5% of total healthcare expenditure was on pharmaceuticals, more than double OECD counterparts, and by 2017 it was predicted to be the world's second largest drug market by value [49]. Although not formally announced or implemented, the National Development and Reform Commission announced in 2015 that multinational companies would need to provide prices of their drugs in the UK, France, the Netherlands, 12 other European countries, the United States, Asia and Africa [43]. A survey by the NDRC earlier in the same year had revealed that although 60% of Chinese drug prices fell within the international price range, half were in the upper half of global drug prices and 20% were most expensive in China [43].

A pilot project in Chongqing province in Southwest China bears some resemblance to ERP policies. In January 2015 it announced that it would be implementing a pricing pilot in all municipal public hospitals that would apply to the 300 top-prescribed molecules and dosage forms. At the time of the review by Chen et al, the province had planned to use both internal reference pricing and a comparison of the procurement price of the product with the national average procurement price (NAPP) [49]. So although this comparison is not with foreign countries, the areas used for comparison within the same country are fairly autonomous.

In assessments of the availability, prices and affordability of WHO essential medicines in Guatemala and Haiti, the investigators of both analyses expressed the comparisons as ratios relative to international reference prices in the form of the 2009 Management Sciences for Health reference prices from the International Drug Price Indicator Guide [50, 51]. In both studies the authors commented on the limitation of using this median price ratio because if the supplier prices are unavailable, buyer prices are substituted and this may result in inaccurately high or low reference prices that aren't a true reflection of the median prices that are paid internationally. In the survey of essential medicines in Guatemala, the authors concluded that the availability was low in both the public and private sectors, but was lowest in the public sector [50]. The private sector is challenged with inconsistent pricing and poor affordability and it was observed that higher priced medicines were 22.67 times more expensive than the international reference price [50]. Generalisation is limited by small sample size as only 6 medicines were included in the price comparison.

The survey of Haitian medicine prices demonstrated that the prices were much higher than the international reference price [51]. Originator brands surveyed in the private sector were 35 times the international reference price. A variability in medicine pricing among outlets in all sectors was observed, possibly as a result of low market competition; a lack of medicine price regulation and supply chain differences [51]. The authors also conducted an international comparison of private sector prices by comparing the median price ratio of the medicines in Haiti, Nicaragua, Mexico, Columbia and Bolivia, and based on these comparisons the medicines were most expensive in Haiti [51].

ERP may have unintended negative effects. The concept of price convergence from external reference pricing from spillover and re-referencing of prices may lead to a resistance by suppliers to offer discounts in low revenue areas. This may translate internationally to a reluctance to offer discounts that are not confidential [49]. Espin et al also noted that spillover from ERP may negatively affect low income countries and they emphasize that empirical research should be conducted to ensure evidence based ERP design, implementation and application [46]. Leopold et al note that countries with high prices may not include ERP as a pricing strategy because parallel trade may have a similar price convergence impact and evoke the same industry launch strategy behaviour [48]. The confidential nature of discounted prices may also limit the positive effect of ERP as these prices would not be included in the comparison [48].

Leopold et al do not agree with the suggestion by Seiter, from the World Bank, that ERP will reach the end of its useful life-cycle [47]. The authors argue Seiter's theory that price differences will diminish as all countries reference each other, with the view that this will be mitigated by countries regularly adjusting their ERP methodologies [47].

Vogler et al conducted bi-annual surveys with European countries to ascertain whether countries that were severely affected by the global financial crisis introduced more policy changes and austerity measures to mitigate the impact of the crisis [52]. They identified two areas of focus for policy-makers, medicine prices and generics. Measures promoting the use of generics were identified including INN prescribing and generic substitution, and changes in generic prices and internal reference price systems. Price cuts and freezes were the most frequently observed policy measures to manage medicine prices. Discount and rebate type measures were also widely used. The authors noted that in the short term, the savings achieved from price cuts and discounts would be similar, but industry would be able to maintain an overall higher price level across countries when offering discounts as opposed to price cuts as the latter would require changes to the published list price for external reference pricing [52].

Leopold et al noted that there is still no consensus on which pharmaceutical policies or interventions, aimed at curbing public spending while simultaneously promoting research and development, are successful [47]. However, the authors note that it is imperative to employ a combination of pricing and volume-control policies and subject them to regular review to prevent the "pendulum effect" from market player adjustment [47].

The 2015 WHO guidelines on country pricing give the following recommendations for external reference pricing [38]:

- Countries should consider using external reference pricing as a method for negotiating or benchmarking the price of a medicine.
- Countries should consider using external reference pricing as part of an overall strategy, in combination with other methods, for setting the price of a medicine.
- In developing an external reference pricing system, countries should define transparent methods and processes to be used.
- Countries /payers should select comparator countries to use for ERP based on economic status, pharmaceutical pricing systems in place, the publication of actual versus negotiated or concealed prices, exact comparator products supplied, and similar burden of disease.

In the second edition of the WHO and Health Action International (HAI) publication on measuring medicine prices, availability, affordability and price components, the authors acknowledge the challenges involved in obtaining reliable pricing information and how this negatively impacts on national policy development and evaluation [53] The ex-manufacturer prices in the private sector are often confidential [53]. The lack of publicly available international medicine pricing data makes it difficult for countries to compare themselves to others and hinders the basis for price negotiation [53].

Where countries do publish pricing information, its use may be limited by country-specific details and need for translation [53].

Internal reference pricing methodologies may provide an opportunity to narrow the price differential between off-patent originators and generics [43]. Samning, a city in Fujian Province is performing a reimbursement cap pilot that commenced in June 2014 on selected drugs that displayed a "minimal difference in terms of quality and a big difference in terms of price". An analysis in 2015 showed that prices decreased significantly and locally produced generics seemed to take the place of imported drugs [49]. Although the Chinese government is motivating for the use of reimbursement caps, the implementation of reimbursement caps is still unclear. The assignment of responsibilities and the methodology for the setting of the reimbursement caps is complicated but there is a suggestion from NDRC communications that costs, quality and winning tender prices may be incorporated into the methodology for the reimbursement levels [43].

2.1.7 Key findings in the articles:

A Cochrane review on pharmaceutical policies including reference pricing concluded that the "effects of other purchasing and pricing policies are uncertain due to sparse evidence" [54]. This was echoed in the limited number of studies retrieved that primarily assessed the impact of international benchmarking on medicine pricing. One specific study retrieved assessed the benchmarking of antiretrovirals in Latin American countries. The authors themselves described their analysis as a "Rare attempt to develop a series of benchmarks that can be used to help procurement agencies identify opportunities to evaluate their procurement efficiencies" [55].

Wirtz et al also concluded that the "best benchmark does not exist" [55]. This resonated from the evidence reviewed as the approach to pricing comparison and the implementation of comparative pricing policies varied among article and country experience. Sample selection, unit of measurement for price and volume, the impact of consumption patterns, exchange rates and purchasing powers have a major impact on pricing comparisons [42].

Another limitation observed was the availability of volume and pricing data. The datasets consisted of small volumes as observations were often excluded if price information was unavailable. This is a complex issue as the lack of pricing data availability may be due to a lack of transparency from pharmaceutical companies, especially where discounts are concerned. Volume data is also lacking, especially in low-income countries. It is of vital importance that reliable procurement data on both price and volumes is maintained [35]. Information on discounts is also confidential and this affects the data [56].

The resounding message from the articles reviewed was the need for the implementation of pricing policies. In the analysis by Srivastava et al, the authors identified the need for pricing policies to combat potential market access restrictions where pharmaceutical companies do not price discriminate on the basis to pay. The authors also observed that pricing policies are not standard in low-income countries, potentially due to the administration costs associated with the implementation of such a policy [35]. In a benchmarking analysis of medicine prices in New Zealand and 16 European countries, the authors concluded that medicine prices in a country are a result of pricing policies and reimbursement strategies [56]. This was also demonstrated in an analysis comparing Ontario generic prices to prices in the US and New Zealand. The authors concluded that even by lowering the price of the generics to 25% of the equivalent brand, which is the lowest in Canada, the prices remained substantially higher than in New Zealand and the US, where competitive mechanisms are implemented [45].

High quality evidence on the long-term effects of pricing policies is limited. Where evidence on the impact of external reference pricing is available, it is limited to country experience or an isolated medicine class comparison which limits the external validity of the observations. Chen et al noted that foreign pricing policies cannot be properly transferred to China without being properly adjusted for local healthcare specificities [49]. Therefore, in addition to a lack of long term outcomes evidence on pricing policies like international reference pricing, the local application of policies used internationally is essentially, experimental. In conclusion, there is limited high quality long-term evidence on the impact of pricing policies, and less in the more specific setting of international benchmarking. Based on the searches in this particular literature review, no evidence regarding the use of international benchmarking on immunosuppressive medicines was retrieved nor was any literature on the impact of external reference pricing on medicine prices in South Africa.

CHAPTER 3

3.1 Paper 1

This article has been submitted to the South African Medical Journal (SAMJ). The manuscript below was formatted according to author guidelines for this journal. Proof of submission of this manuscript to the South African Medical Journal can be found in annexure B.

Title:
The impact of international benchmarking on the price of immunosuppressive medicines for transplant recipients in South Africa.

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Ethical clearance number - HSS/0154/013 (University of KwaZulu-Natal)

Title
The impact of international benchmarking on the price of immunosuppressive medicines for transplant recipients in South Africa.

Abstract
Background

The use of external reference pricing (ERP) is an internationally applied pricing policy used to regulate the price of medicines. In 2005, the South African Minister of Health published a government gazette of regulations relating to a transparent pricing system for medicines and scheduled substances and it stated that the Minister must publish a methodology for conforming to international benchmarks. In May 2014, the most recent proposed benchmark methodology was published detailing that international benchmarking of medicines (IBM) requires that the lowest price in a selected basket of countries (Australia, Canada, New Zealand, Spain and South Africa) be used as the ultimate price for the purposes of benchmarking of originator products.

Objectives

This study aimed to provide a broad observational basis for the use of IBM and the proposed countries as a pricing tool; the feasibility of using BRICS countries as comparator countries; and a small sample comparison of local state tender pricing in relation to the IBM gazette benchmarking pricing. Immunosuppressant medicines for organ transplant patients were used for this comparison as they are relatively high cost and there is reluctance to implement pricing and reimbursement policy options to contain costs of these medicines.

Methods

Ex-manufacturer medicine pricing information for 2016, 2017 and 2018 was sourced for immunosuppressive medicines for South Africa (public and private sectors), Australia, New Zealand, Canada, Spain, Brazil, Russia. Unit prices were compared for products with the same INN, strength, formulation and manufacturer. In most cases the groups were matched on product name, bearing in mind translation nuances.

Results

Across all three years, in the majority of groups, external reference pricing using the Gazette methodology benchmark countries Australia; New Zealand; Canada and Spain, lowered the local private sector ex-manufacturer price of medicine. Similarly, in the majority of groups comparing local pricing to that of available BRICS country pricing data, the comparison lowered the price. In 92% of groups where a comparison could be made, the South African state tender price was the lowest available price.

Conclusion

Conducting an external reference pricing analysis is time and resource consuming. However it may prove to reduce a current or proposed medicine price and may be considered as one of a variety of medicine pricing policies employed by a country. It should not be used in isolation of other medicine pricing and reimbursement policies

Conflicts of interest – none

Introduction/background

According to the Council for Medical Schemes' Annual report for 2017/2018, 16.08% of total benefits paid by medical schemes in 2017 were for medicines [1]. This high percentage of spend on medicines in the medical insured population in South Africa highlights the importance of medicine price regulation and the need for robust tools and policies to contain costs in order to manage resources. In 2005, the South African Minister of Health published a government gazette of regulations relating to a transparent pricing system for medicines and scheduled substances [2]. The Single Exit Price (SEP) legislation detailed in this gazette aimed to regulate medicine pricing and remove the practice of discounts and rebates where benefits were not reaped by consumers [3]. Initially when implemented, the SEP had a significant impact on the price of medicines and medicine expenditure but over time a rebound in pricing was observed [3]. However the SEP implementation was only intended to be the first phase of addressing medicine price concerns at the ex-manufacturer level [3]. To address the second phase, it was noted in the 2005 Gazette that the Minister must publish in the Gazette, a methodology for conforming to international benchmarks. In December 2006 the initial methodology for international benchmarking of the prices of medicines and scheduled substances in South Africa was published for comment [4]. In December 2010, a subsequent detailed proposed methodology addressing commentary was published for further comment [3]. In May 2014, the most recent proposed methodology for regulations relating to a transparent pricing system for medicines and scheduled substances (benchmark methodology) was published [5].

"The *aim* of international benchmarking, together with other regulatory interventions, is to: *Protect the South African health system from paying distorted prices for medicines through the elimination of price distortions and price distorting behaviour."* [3]. The Pricing Committee

and the National Department of Health wish to establish a programme in South Africa that involves negotiating drug prices that relate to their therapeutic performance but also takes in to account socioeconomic factors [5]. The proposed methodology for international benchmarking of medicines (IBM), referred to internationally as external reference pricing (ERP), requires that the lowest price in a selected basket of countries be used as the ultimate price for the purposes of benchmarking. The selected basket of countries includes Australia, Canada, New Zealand, Spain and South Africa [5]. The Department of Health may review the basket every two years and a possible complementary list of benchmark countries may be published online [5].

Evidence regarding the impact of different pricing policies on medicine prices, especially in low income countries, is scarce. This issue is twofold as it refers not only to a lack of evidence but also a potential lack of successful pricing policy implementation [6, 7]. Literature assessing whether medicine prices would be lowered on implementation of this IBM/ERP policy are lacking.

Furthermore, the current proposed basket of countries were selected on the basis of pre-specified criteria selecting countries with effective systems for pricing and regulating medicines [3]. However their health system structure and socio-economic background may be considered significantly different from that of South Africa. As emerging economies, BRICS countries may pose as more suitable economic comparators, however literature on the use of BRICS countries as external reference pricing countries is also lacking.

The South African state sector is currently not subject to the SEP legislation and makes use of tender processes to procure medicines by means of volume-based purchasing [8]. A secondary analysis aimed to provide insight into whether state tender prices remain consistently low when compared to private sector South African medicine prices and the Gazette benchmarking countries.

The purpose of this observational analysis was to determine whether the implementation of the proposed methodology for IBM would have a positive (cost saving) impact on the prices of immunosuppressive medicines for transplant patients. The primary comparison aimed to assess the whether the application of IBM with the Gazette benchmark countries would lower the price of medicines locally. The secondary analysis aimed to assess whether using BRICS countries as a benchmark would lower the local price of medicine. Furthermore, a comparison of the South African government sector tender prices with the five Gazette benchmark countries (South Africa private sector, Australia, Canada, New Zealand, Spain) aimed to assess whether state tender prices are the lowest.

Internal reference pricing as a cost minimisation tool may not be considered a feasible tool to implement for this particular group of medicines, but international benchmarking may provide an alternative mechanism to lower the cost of medicines in this group in a manner that does not directly involve the person using the medicine.

Overall this study aimed to provide a broad observational basis for the use of IBM and the proposed countries as a pricing tool, the feasibility of using BRICS countries as comparator countries, and a small sample comparison of local state tender pricing in relation to the IBM gazette benchmarking pricing.

Methods

Selection of medicines

Immunosuppressants used to prevent graft rejection were selected from the Anatomical Therapeutic Classification (ATC) class L04A – Immunosuppressants. As this list is exhaustive and not exclusive to medicines used to prevent graft rejection, local and international registration status was determined to isolate the International Non-proprietary Name (INN) products used in this setting. Products registered locally or by the FDA or EMA were included in the list for the sourcing of pricing information.

Time frame of medicine pricing information

An attempt to obtain pricing information for 2016, 2017 and 2018 for all comparator countries was made.

Data sources

In accordance with the specifications of the Gazette methodology, the ex-manufacturer prices exclusive of VAT were sourced. Publicly available sources of ex-manufacturer pricing was obtained for Australia, Canada, New Zealand, Spain, South Africa (private sector ex-manufacturer and state tender), Brazil and Russia.

The National Pharmaceutical Pricing Authority of the Government of India provides an online public pricing resource of scheduled formulations, http://nppaimis.nic.in/nppaprice/newmedicinepricesearch.aspx, but as the price is regulated at the maximum retail price and that is the published price, no public resource of regulated ex-manufacturer pricing was found. A resource of state tender pricing http://www.tnmsc.com/tnmsc/new/index.php was also found but would not be an appropriate comparator for this benchmarking analysis.

Although a reform of the price setting of medicine in China is underway [9], no formal publicly available resource of medicine pricing was found. The China Drug and Food Administration drug database does not include pricing(http://app1.sfda.gov.cn/).

Australia

Ex-manufacturer pricing information was sourced from the PBS website on the following link: http://www.pbs.gov.au/info/industry/pricing/ex-manufacturer-price. Current and historic pricing information was available in Excel spreadsheet format and the ex-manufacturer price captured was that of the column entitled AEMP. Pricing spreadsheets as of 01/08/2016, 01/08/2017 and 01/04/2018 were used for the 2016, 2017 and 2018 pricing information respectively.

Canada

Pricing information was obtained from the Alberta Drug Benefit List on the Alberta Health website on the following link: https://www.ab.bluecross.ca/dbl/publications.html. Spreadsheets were available for download and historic pricing information for the last five months was available on the website. An interactive online price per unit search tool is now available on this webpage. Contact was made with the with the Pharmaceutical Product and Pricing Administration team of the Alberta Blue Cross on the email address WADBL@ab.bluecross.ca to confirm that the pricing available on the spreadsheets was the ex-manufacturer price. Confirmation was received as follows "The prices published in the Alberta Drug Benefit list (ABDL) are the ex-factory prices, that is, they are the manufacturer's price without any wholesaler specific upcharges or distribution costs of those drug products covered under the Alberta government sponsored coverage. The prices are also the reimbursable price,

except where the Least Cost Alternative (LCA) or Maximum Allowable Cost (MAC) pricing applies." The team also confirmed that if a product was not a benefit on the ADBL (government sponsored) it would not be covered through any special application. They added that there may be a benefit on their private sponsored drug programmes and the price list that would apply would be the ABCDPL Alberta Blue Cross Drug Price List. The team also provided the spreadsheets that were not available on the website at the time. The ADBL and ABCDPL lists for August 2016, August 2017 and April 2018 were used to capture the per unit pricing information. Off patent originator and generic medicine pricing is not directly regulated in Canada but patent medicine pricing is regulated by the Patent Medicines Pricing Review Board (PMBRB). Slight variations in the price of patented medicine across jurisdictions in Canada is linked to mark-up policies which are accessible on http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1312&lang=en, but for up to date information it would be important to confirm with each formulary body directly. Due to accessibility and engagement with the Alberta Blue Cross, pricing from Alberta was used for this analysis, but it must be noted that this pricing may not be identical throughout all jurisdictions due to mark-up polices, although there should be minimal variation in ex-manufacturer pricing due to PMPRB regulation.

New Zealand

Ex-manufacturer pricing information was sourced from the PHARMAC website on the following link: https://www.pharmac.govt.nz/tools-resources/pharmaceutical-schedule/. Current and historic pricing information was available in PDF format with an explicit column stipulating the ex-manufacturer price. Schedules for August 2016, August 2017 and April 2018 were used for the 2016, 2017 and 2018 pricing information respectively.

Spain

Pricing information was sourced from the Ministry of Health, Consumer Affairs and Social Welfare website on the following link: https://www.msssi.gob.es/en/profesionales/nomenclator.do which has subsequently been redirected to: https://www.mscbs.gob.es/en/profesionales/nomenclator.do. A search tool for current pricing information was available in Spanish and a search for the available products and their pricing was conducted by searching by INN ("Principio active"). Pricing information was obtained for April 2018. Despite multiple attempts to obtain historic pricing information from the Spanish authorities and academics in Spain, the pricing information for 2016 and 2017 was not obtained. The PVP (precio de venta al public) pricing, the price at which the medication is sold to the public, obtained from the search tool was manipulated to remove 4% IVA (VAT), and then converted to the ex-manufacturer price (PVL – precio industrial maximo de los medicamento) by means of a published conversion formula (Annexure A).

Brazil

Pricing information was sourced from the Brazilian Health Regulatory Agency (ANVISA) website on the following link: http://portal.anvisa.gov.br/listas-de-precos. The website is in Portuguese and current and historic ex-factory and public purchase pricing information was available in separate documents in either PDF or Excel format. Pricing information from 2003 was available on this site. Spreadsheets dated 19th August 2016, 22nd August 2018 and 14th March 2018 were used for the 2016, 2017 and 2018 pricing information respectively. The Preço Fábrica (PF 0% column) was captured.

Russia

Pricing information was sourced from the Russian State Register of Medicines (Государственный реестр лекарственных средств) website on the following link: http://grls.rosminzdrav.ru/PriceLims.aspx?Torg=&Mnn=&RegNum=&Mnf=&Barcode=&Order=&isActual=0&All=0&PageSize=8&orderby=pklimprice&orderType=desc&pagenum=1. The information was available in an Excel spreadsheet and PDF format and was sorted by INN (MHH). Alternatively the search tool functionality was also available to search for products of a particular INN. As the website and spreadsheets are in Russian, and therefore the Cyrillic script, Google translate was used to convert the information to English in the Latin script. Multiple emails were sent to the contact details on the spreadsheet requesting assistance with no response. However, assistance was obtained from a contact working in a medicine access organisation in Russia who confirmed that the pricing specified in the spreadsheet was the ex-manufacturer price and that column I stipulated the most recent pricing update.

Pricing

In line with the Gazette methodology medicine prices were converted to South African Rands (ZAR) using the average currency exchange rate for the particular currency for the past twelve months. Historical exchange rate data were obtained from the South African Reserve Bank website on the following link: https://www.resbank.co.za/Research/Rates/Pages/SelectedHistoricalExchangeAndInterestRates.aspx. The time ranges of historical data exported were for the 1st January 2016 to 31st December 2016; 1 January 2017 to 31 December 2017; 1 June 2017 to 31 May 2018. The ranges were exported in Excel formal and an average conversion rate for the time range was calculated in Excel.

Sorting process

Data lines were matched on the basis of the same INN, strength, formulation and manufacturer. In most cases the groups were matched on product name, bearing in mind translation nuances. Where products were matched on all of the listed criteria but the trade name varied (e.g Mycocept® and Mycophenolate Sandoz®) they were still grouped together. Different pack sizes were included in the same group and in all cases pricing was compared on unit price level. Generic product groups were not excluded, however only groups where South African private sector pricing was included were assessed.

The Government Gazette 37625 Regulations relating to a transparent pricing system for medicines and scheduled substances (benchmark methodology) published in May 2014 states that the IBM methodology will apply to all originator medicines for which there are less than 2 generic competitors. On completion of this phase of implementation, it is the intention of the Minister of Health to address the methodology for originator medicines with 2 or more generic competitors and generic medicines. For the purposes of this analysis, groups were not included or excluded on this basis.

Assessment of groups

Groups were analysed per year using six key questions:

A. Would benchmarking against the four countries listed in the Gazette (Australia, New Zealand, Canada and Spain) decrease the South African medicine price?
   In how many groups did benchmarking against these countries lower the price?

B. Is the full benchmarking basket available (Australia, New Zealand, Canada and Spain)?
C. Which benchmarking country has the lowest price (by frequency)?
D. Would benchmarking against the remaining BRICS countries decrease the South African medicine price?
E. Which BRICS country has the lowest price (by frequency)
F. Is the state tender pricing lower than all Gazette benchmark countries - in groups where state tender prices are available, in how many groups was the state tender price the lowest price compared to the 5 Gazette benchmark countries?

Results

Pricing information was sourced for products containing ciclosporin, mycophenolate mofetil, mycophenolic acid, sirolimus, tacrolimus, everolimus, azathioprine and equine gamma globulin.

Table 1 presents a summary of the results. As can be seen from this table, using pricing data from 2016, 2017 and 2018, a total of 78 IBM immunosuppressant groups were analysed in accordance with the Gazette methodology stipulating that the lowest price in the group must become the benchmark price. Due to a more limited number of appropriate product pricing matches, a smaller number of groups, 66, were analysed using the same methodology but with BRICS countries as comparators. The application of the IBM methodology lowered the South African private sector ex-manufacturer price in 68%, 85% and 85% of groups in 2016, 2017 and 2018 respectively. In only one group across all three years was the full benchmarking set of country data available and in that group, Spain had the lowest price listed (Pfizer Rapamune® sirolimus 1mg tablet). Australia was consistently the lowest country by frequency of lowest price, however where New Zealand pricing was available it demonstrated the largest average percentage decrease of price by a benchmarking country consistently in 2016 (60%), 2017 (53%) and 2018 (56%).

Of the BRICS countries, ex-manufacturer pricing data was obtained for Brazil and Russia. By comparison against these two countries, the South African private sector ex-manufacturer price was lowered in 81%, 90%, 81% of groups where a comparator price was available in 2016, 2017 and 2018 respectively. In the majority of groups in 2016, 2017 and 2018, Russia had the lowest price frequency.

Where a South African state tender price was available for a group, it was compared to the IBM countries' pricing where available, including the South African private sector ex-manufacturer price. 38 groups were assessed for this comparison. In each year, in 92% of groups where a comparison could be made, the South African state tender price was the lowest available price.

			2016	2017	2018
	Number of IBM benchmarking groups		25	27	26
A	Number of groups where IBM gazette lowered price		17	23	22

	Percentage number of groups where IBM gazette lowered price		68%	85%	85%
B	Full benchmarking country set		0	0	1
	Groups with 3/4 countries plus SA		7	7	9
	Groups with 2/4 countries plus SA		13	16	14
	Groups with 1/4 countries plus SA		5	4	2
	No price change (South Africa lowest)		8	4	4
	Percentage groups with no price change		32%	15%	15%
C	Lowest priced country by frequency	Australia	11	14	12
		New Zealand	6	8	8
		South Africa	7	4	4
		Canada	1	1	1
		Spain	0	0	1
	BRICS groups		21	21	21
D	Price lowered by comparator countries		17	19	17
	% number of groups where BRICS comparator lowered price		81%	90%	81%
E	Lowest priced country frequency	Russia	13	18	16
		Brazil	4	1	2
		South Africa	4	2	3
F	In groups where state tender prices are available,	Groups available	13	13	12
	In how many groups were state tender prices the lowest price compared to all 5 benchmark countries incl. SA	Lowest	12	12	11
	% number of groups where South African state tender price was the lowest price compared to all 5 benchmark countries incl. SA		92%	92%	92%
	Average percentage decrease per country (*in groups where decrease seen)	Australia	27% (n=11)	35% (n=14)	37% (n=12)
		New Zealand	60% (n=6)	53% (n=6)	56% (n=8)
		Canada	2% (n=1)	16% (n=1)	18% (n=1)
		Spain	n=0	n=0	30% (n=1)

Table 1. Summary of results

Table 2 presents a summary of the medicine groups assessed for each comparison. In all three groups the originator groups that included only BRICS comparators were Novartis Simulect® (basilixmab) 20mg vial and Astellas Prograf® (tacrolimus) 5mg/ml 1 ml injection.

Comparisons					Gazette benchmarking countries			BRICS			State tender		
Name	**Generic name**	**Formulation**	**Strength**	**Unit comparison**	**2018**	**2017**	**2016**	**2018**	**2017**	**2016**	**2018**	**2017**	**2016**
Novartis Sandimmun	Ciclosporin	1ml ampoules	50mg/ml	1ml	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Novartis Sandimmun	Ciclosporin	oral solution 50ml	100mg/ml	1ml	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Novartis Neoral	Ciclosporin	capsules	100mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sandoz Ciclohexal	Ciclosporin	capsules	100mg	1 capsule	Yes	Yes	No	No	No	No	No	No	No
Novartis Neoral	Ciclosporin	capsules	25mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sandoz Ciclohexal	Ciclosporin	capsules	25mg	1 capsule	Yes	Yes	No	No	No	No	No	No	No
Roche Cellcept	Mycophenolate mofetil	intravenous infusion	500mg	1 vial	Yes	Yes	Yes	No	No	No	No	No	No
Roche Cellcept	Mycophenolate mofetil	oral suspension	200mg/ml	1ml	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Roche Cellcept	Mycophenolate mofetil	capsules	250mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Novartis Myfortic	Mycophenolic acid	enteric coated tablets	180mg	1 tablet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Novartis Myfortic	Mycophenolic acid	enteric coated tablets	360mg	1 tablet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Roche Cellcept	Mycophenolate mofetil	tablets	500mg	1 tablet	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Sandoz mycophenolate	Mycophenolate mofetil	tablets	500mg	1 tablet	Yes	Yes	Yes	No	No	No	No	No	No
Sandoz mycophenolate	Mycophenolate mofetil	capsules	250mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Pfizer Rapamune	Sirolimus	tablets	1mg	1 tablet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Novartis Simulect	Basiliximab	vial for injection	20mg	1 vial	No	No	No	Yes	Yes	Yes	No	No	No
Astellas tacrolimus	Tacrolimus	injection	5mg/ml	1ml	No	No	No	Yes	Yes	Yes	No	No	No
Astellas Prograf	Tacrolimus	capsules	5mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Astellas Advagraf XL	Tacrolimus	capsules	5mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Astellas Prograf	Tacrolimus	capsules	1mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Astellas Advagraf XL	Tacrolimus	capsules	1mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Astellas Prograf	Tacrolimus	capsules	0.5mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Astellas Advagraf XL	Tacrolimus	capsules	0.5mg	1 capsule	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Novartis Certican	Everolimus	tablets	0.75mg	1 tablet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Novartis Certican	Everolimus	tablets	0.25mg	1 tablet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Aspen Imuran	Azathioprine	injection	50mg	1 vial	Yes	Yes	Yes	No	No	No	No	No	No
Aspen Imuran	Azathioprine	tablets	50mg	1 tablet	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Amneal/Litha Azamun	Azathioprine	tablets	50mg	1 tablet	No	Yes	Yes	No	No	No	No	Yes	Yes
Pfizer Atgam	Equine gamma globulin	ampoule	50mg/ml	1ml	Yes	Yes	Yes	No	No	No	No	No	No

Table 2. Summary of groups for each comparison

Discussion

This observational analysis of immunosuppressant medicines showed that in the majority of groups, external reference pricing using the Gazette methodology benchmark countries Australia; New Zealand; Canada and Spain, lowered the price of the medicine. Similarly, in the majority of groups comparing local pricing to that of available BRICS country pricing data, the comparison lowered the local private sector ex-manufacturer price of medicine.

Historic information for Spanish medicine pricing was not available. Therefore only pricing for 2018 was available for capturing and comparison. The 2018 group for Pfizers' Rapamune® (sirolimus) 1mg tablets was the only reference price group where information was available for all five benchmarking countries including Australia, New Zealand, Canada, Spain and of course, South Africa. Most groups had pricing for South Africa and two other reference price countries. Most frequently, Australia had the lowest price in the IBM comparison groups, however where available, New Zealand pricing consistently demonstrated the largest average percentage decrease of price (average decrease of 56% in 20 groups).

Although not listed as part of the Gazette's benchmarking countries [2], the aim of including BRICS countries as a separate assessment was to compare pricing in emerging markets considered more economically similar to South Africa. This analysis was limited by the availability of regulated medicine pricing information in India and China. Information for current and historic Brazilian medicine pricing was freely and clearly accessible online and could be translated from Portuguese to English using Google Translate. Ex-manufacturer pricing information could be downloaded in Excel or PDF format and could be filtered, facilitating the sourcing of appropriate comparator pricing information. Similarly Russian online medicine pricing information also required the use of Google Translate. However, the added complication of a different alphabet made this translation less intuitive, and made the identification of appropriate comparator pricing information more tedious than with the Brazilian comparison. Among the three BRICS countries included in the analysis, Russian pricing was most frequently the lowest. Therefore although the use of Russia as a comparator country for South Africa may appear favourable on the basis of this analysis, results should be used with caution as attempts to verify pricing information with the Russian State Register of Medicines were not successful. A concern is that the pricing information may be out of date and may not be a true reflection of the actual current ex-manufacturer pricing in Russia.

South African state tender pricing information was not available for all IBM groups but where it was, it had the lowest price in 92% of groups (n=38). The discrepancy between the South African private sector ex-manufacturer medicine pricing and the South African state sector pricing is driven by volume based pricing negotiations in the form of state tenders [8]. This assessment, although limited by sample size, should prompt the discussion that external reference pricing in isolation may not generate as favourable medicine pricing as would either volume based pricing or a combination of the two policies.

Limited by small sample size and ATC, this analysis has shown that IBM using Australia, New Zealand, Canada and Spain would lower the price of the majority of medicines in this immunosuppressant analysis. It is important to explore why these comparator countries may be generating more favourable medicine pricing than the private sector in South Africa. Spain, Australia and New Zealand all include a form of internal reference pricing in their national reimbursement policies and although Canada does not directly regulate off-patent originator and generic pricing [3], outpatient prescriptions are reimbursed by private insurers who may decide to employ a form of internal reference pricing. Although the use of generic reference pricing of immunosuppressant medicines in transplant recipients is a complex issue, and where implemented may be done with tight controls to avoid switching among products [10], the use of internal reference pricing by comparator countries does once again highlight the importance of a multi-dimensional approach to the pricing of medicines in general.

Noted challenges of the observational analysis included access and availability of current and historic pricing data, comprehension of the data available and its applicability within the context of the specific country and the matching of products for comparison. The medicine pricing information from a comparator country may be meaningless if not used with an understanding of the pricing and reimbursement policies, taxation structures and health care funding employed in that specific country. In addition to this, a medicine's price has a specific local history that affects pricing and includes patent expiry timing and subsequent launch of competitor generics to the market. Medicine prices may be compared across countries at a specific point in time when on- and off-patent market factors may differ. Similarly, the emergence of negotiated confidential discounts and pricing for patient access schemes may affect the transparency of the published medicine pricing and its use in an external reference pricing comparison. The Gazette methodology explicitly details how products should be grouped for comparison [2, 3, 4, 5], however the reality of the application of this methodology is a challenge and often requires further investigation and occasionally a degree of assumption. For example, a product may match on most factors including trade name, manufacturer and strength but the publicly available medicine pricing database of one country may list the formulation as a tablet and another country may list is as a film coated tablet. Furthermore, the complex nature of the pharmaceutical industry involving mergers, local marketing or distribution licences may also complicate confirmation of the same manufacturer source.

The main limitation of this observational analysis is the small sample size and restriction to one therapeutic medicine group, immunosuppressants for organ transplant rejection. The analysis did not attempt to ascertain whether the local registered price of the medicine was already subject to the proposed benchmarking methodology and whether this may have contributed to the reason South Africa had the lowest price in certain groups.

Since the commencement of this observational analysis, the Euripid Collaboration and the EU Health Progam have published twelve guiding principles for external reference pricing. In July 2018 they published these twelve principles in a guidance document with the aim of "coordinating approach of national authorities regarding the use of ERP to avoid/mitigate negative impact for patient access to medicines" [11]. Although this document has been developed in a European context, the principles should be considered by any country considering or revising an international benchmarking policy.

Conclusion

The use of external reference pricing is an internationally applied pricing policy used to regulate the price of medicines. It should not be used in isolation of other medicine pricing and reimbursement policies [11]. As can be seen in this analysis, both the use of external reference pricing and comparison with the price derived from volume-based pricing in the form of state tenders has the potential to lower the local cost of medicine in the private sector.

High quality evidence on the long-term effects of pricing policies is limited. Where evidence on the impact of external reference pricing is available, it is limited to country or European experience or an isolated medicine class comparison which limits the external validity of the observations.

Conducting an external reference pricing analysis, even of one product, is time and resource consuming. However as shown in this small analysis, it may prove to reduce a current or proposed medicine price. It may also provide an opportunity for reflection on how comparator countries are approaching medicine pricing and provide insights for constant local improvement and dynamic medicine pricing policies.

Published medicine pricing information should be updated at regular intervals; clearly stipulate the points at which the medicine price is regulated within the local context; and clarify the applicable taxes that are included or would be added to the published medicine price. Resources should clearly state to which sector the published medicine pricing information applies. As more countries begin to publish medicine pricing information online, the South African basket should be regularly reviewed in order to potentially expand the list of included countries.

Collaboration among countries to share pricing resources and enhance the benefit derived from external reference pricing methodologies and other pricing policies, should be promoted to facilitate improved access to medicine.

References

1. CMS Annual Report Annexures 2017/2018. South Africa: The Council for Medical Schemes; 2018. 62 p.
2. Tshabalala-Msimang, M. Government Gazette Regulations relating to a transparent pricing system for medicines and scheduled substances. Government Printing Works; 2005. Gazette 28214
3. Motsoaledi, A. Government Gazette Regulations relating to a transparent pricing system for medicines and scheduled substances (Methodology for international benchmarking of prices of medicines and scheduled substances in South Africa). Government Printing Works; 2010. Gazette 33878.
4. Tshabalala-Msimang, M. Government Gazette Regulations relating to a transparent pricing system for medicines and scheduled substances (Methodology for international benchmarking of the prices of medicines and scheduled substances in South Africa). Government Printing Works; 2006. Gazette 29443
5. Motsoaledi, A. Government Gazette Regulations relating to a transarent pricing sstem for medicines and scheduled substances: Benchmark methodology. Government Printing Works, 2014. Gazette 37625.

6. Srivastava D, McGuire A. Analysis of prices paid by low-income countries-how price sensitive is government demand for medicines?. BMC public health. 2014 Dec;14(1):767. DOI:10.1186/1471-2458-14-767
7. kwabena Tetteh E. Providing affordable essential medicines to African households: the missing policies and institutions for price containment. Social science & medicine. 2008 Feb 1;66(3):569-81. DOI:10.1016/j.socscimed.2007.10.003
8. Department of Health. Tenders [Internet]. South Africa: 2018 [cited 2018 September 30]. Available from http://www.health.gov.za/index.php/2015-05-15-12-36-34
9. Fang Y. Pharmaceutical pricing policies in China. In: Baber ZUD. Pharmaceutical Prices in the 21st Century. Springer International Publishing Switzerland; 2015. DOI 10.1007/978-3-319-12169-7_3
10. Allard J, Fortin MC. Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients? Canadian Journal of Kidney Health and Disease. 2014 Dec;1(1):23.
11. Habl C, Schneider P, Németh G, Šebesta R. Euripid Guidance Document on External Reference Pricing (ERP).

CHAPTER 4

4.1 Conclusion

The use of external reference pricing is an internationally applied pricing policy used to regulate the price of medicines. It should not be used in isolation of other medicine pricing and reimbursement policies [57].

High quality evidence on the long-term effects of pricing policies is limited. Where evidence on the impact of external reference pricing is available, it is limited to country or European experience or an isolated medicine class comparison which limits the external validity of the observations.

Conducting an external reference pricing analysis, even of one product, is time and resource consuming. However as shown in this small analysis, it may prove to reduce a medicine price. It may also provide an opportunity for reflection on how comparator countries are approaching medicine pricing and provide insights for constant local improvement and dynamic medicine pricing policies. Collaboration among countries to share resources and enhance the benefit derived from external reference pricing methodologies and other pricing policies, should be promoted to facilitate improved access to medicine.

4.2 Recommendations

Collaboration among countries to share explicit medicine pricing information and enhance the benefit derived from external reference pricing methodologies and other pricing policies, should be promoted to improve access to affordable medicine.

Published medicine pricing information should be updated at regular intervals and should clearly stipulate the points at which the medicine price is regulated within the local context. Published medicine prices should clarify the applicable taxes that are included or would be added to the published medicine price. Health systems vary among countries and if a medicine price would differ between or among sectors in a country, resources should clearly state to which sector the published medicine pricing information applies.

As international medicine pricing information becomes more easily accessible, it will allow regulators to increase the number of countries in the basket used for benchmarking or back-up benchmarking. This may provide a broader international reference of medicine prices in countries with a similar economic position.

South Africa should continue to include countries in the benchmarking basket on the basis of the Gazette specified criteria. As more countries begin to publish medicine pricing information online, the basket should be regularly reviewed in order to potentially expand the list of included countries. On the basis of this case study, the National Medicines Pricing Committee should consider reviewing Brazil for inclusion in the benchmarking basket.

Continuous review and reflection on the impact of implemented pricing policies, even on a small ATC class scale, should be conducted and shared.

REFERENCES FOR INTRODUCTION AND LITERATURE REVIEW

1. CMS Annual Report Annexures 2017/2018. South Africa: The Council for Medical Schemes; 2018. 62 p.
2. Motsoaledi, A. Government Gazette Regulations relating to a transparent pricing system for medicines and scheduled substances (Methodology for international benchmarking of prices of medicines and scheduled substances in South Africa). Government Printing Works; 2010. Gazette 33878.
3. Tshabalala-Msimang, M. Government Gazette Regulations relating to a transparent pricing system for medicines and scheduled substances. Government Printing Works; 2005. Gazette 28214
4. Tshabalala-Msimang, M. Government Gazette Regulations relating to a transparent pricing system for medicines and scheduled substances (Methodology for international benchmarking of the prices of medicines and scheduled substances in South Africa). Government Printing Works; 2006. Gazette 29443
5. Motsoaledi, A. Government Gazette Regulations relating to a transarent pricing system for medicines and scheduled substances: Benchmark methodology. Government Printing Works, 2014. Gazette 37625.
6. South African Renal Society. Practice guidelines, statement on use of generic immunosuppressant drugs [Internet]. South Africa: [cited 2018 December 27]. Available from: http://sa-renalsociety.org/guidelines/
7. Allard J, Fortin MC. Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients? Canadian Journal of Kidney Health and Disease. 2014 Dec;1(1):23.
8. Vogler S, Paris V, Ferrario A, Wirtz VJ, de Joncheere K, Schneider P, Pedersen HB, Dedet G. How can pricing and reimbursement policies improve affordable access to medicines? Lessons learned from European countries. Applied health economics and health policy. 2017 Jun 1;15(3):307-21.
9. Government of South Africa. Health [Internet]. South Africa: 2018 [cited 2018 September 30]. Available from: https://www.gov.za/about-SA/Health#schemes
10. Motsoaledi, A. Government Gazette National Health Insurance Bill. South Africa: Government Printing Works, 2018. Gazette: 41725
11. South African Health Products Regulatory Authority. SAHPRA Home [Internet]. South Africa: 2018 [cited 2018 September 30]. Available from: http://www.sahpra.org.za/
12. Department of Health. South African Medicine Price Registry Published documents [Internet]. South Africa: 2018 [cited 2018 September 30]. Available from: http://www.mpr.gov.za/Default.aspx

13. Department of Health. Tenders [Internet]. South Africa: 2018 [cited 2018 September 30]. Available from http://www.health.gov.za/index.php/2015-05-15-12-36-34
14. Government of Canada. Canada Health Act [Internet]. Canada: 2017 [cited 2017 October 31]. Available from: https://www.canada.ca/en/health-canada/services/health-care-system/canada-health-care-system-medicare/canada-health-act.html
15. CADTH. Common drug review [Internet]. Canada: 2017 [cited 2017 October 31]. Available from: https://www.cadth.ca/about-cadth/what-we-do/products-services/cdr
16. Patented Medicine Prices Review Board. PMPRB Compendium of Policies, Guidelines and Procedures [Internet]. Canada: 2017 [cited 2017 October 31]. Available from: http://www.pmprb-cepmb.gc.ca/view.asp?ccid=492
17. García-Armesto S, Begoña Abadía-Taira M, Durán A, Hernández-Quevedo C, Bernal-Delgado E. Spain: Health System Review. Health systems in transition. 2010; 12(4):1–295
18. Bernal-Delgado E, García-Armesto S, Oliva J, Sanchez FM, Repullo JR, Peña-Longobardo LM, Ridao-López M, Hernández-Quevedo C. Spain: Health System Review. Health systems in transition. 2018 May;20(2):1-79.
19. New Zealand Immigration. Healthcare [Internet]. New Zealand: 2017 [cited 2017 December 5]. Available from: https://www.newzealandnow.govt.nz/living-in-nz/healthcare
20. Ministry of Health. Statutory framework [Internet]. New Zealand: 2017 [cited 2017 December 5]. Available from: http://www.health.govt.nz/new-zealand-health-system/overview-health-system/statutory-framework
21. The Treasury. Commercial Portfolio [Internet]. New Zealand: 2017 [cited 2017 December 5]. Available from: https://treasury.govt.nz/information-and-services/commercial-portfolio-and-advice/commercial-portfolio
22. Medsafe. Welcome to Medsafe [Internet]. New Zealand: 2017 [cited 2017 December 6]. Available from: http://www.medsafe.govt.nz/
23. PHARMAC. Our Place in the health system [Internet]. New Zealand: 2017 [cited 2017 December 6]. Available from: https://www.pharmac.govt.nz/about/your-guide-to-pharmac/factsheet-03-our-place-in-the-health-system/
24. Australian Government Department of Human Services. Medicare services [Internet]. Australia: 2017 [cited 2017 December 17]. Available from: https://www.humanservices.gov.au/individuals/subjects/medicare-services

25. ISPOR. Australia Pharmaceutical Global Health Technology Assessment Roadmap [Internet]. 2015 [cited 2018 January 2]. Available from: https://tools.ispor.org/HTARoadMaps/Australia_Pharm.asp
26. Medicare Benefits Schedule Online. What legislation covers the MBS [Internet]. Australia: 2018 [cited 2018 January 2]. Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/faq-legislation
27. Australian Government Department of Health. National Medicines Policy [Internet]. Australia: 2018 [cited 2018 January 2]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/National+Medicines+Policy-1
28. Therapeutic Goods Administration. TGA Basics [Internet]. Australia: [cited 2018 January 2]. Available from: http://www.tga.gov.au/tga-basics
29. Pharmaceutical Benefits Scheme. About the PBS [Internet]. Australia: 2017 [cited 2017 December 17]. Available from: http://www.pbs.gov.au/info/about-the-pbs
30. BRICS 2018 [Internet]. South Africa: 2018 [cited 2018 September 30]. Available from http://www.brics2018.org.za/
31. Harmer A, Fleck F. The BRICS countries: a new force in global health?.
32. Patented Medicine Prices Review Board. Price Review [Internet]. Canada: 2017 [cited 2017 October 31]. Available from: http://pmprb-cepmb.gc.ca/en/regulating-prices/price-review
33. PHARMAC. Medicines and medical devices contract negotiation [Internet]. New Zealand: 2018 [cited 2018 September 30]. Available from: https://www.pharmac.govt.nz/about/your-guide-to-pharmac/factsheet-05-contract-negotiation/
34. Paris V, Belloni A. Value in pharmaceutical pricing country profile: Australia. OECD Health Working Papers; 2014 Nov.
35. Srivastava D, McGuire A. Analysis of prices paid by low-income countries-how price sensitive is government demand for medicines?. BMC public health. 2014 Dec;14(1):767.
36. kwabena Tetteh E. Providing affordable essential medicines to African households: the missing policies and institutions for price containment. Social science & medicine. 2008 Feb 1;66(3):569-81.
37. Rietveld AH, Haaijer-Ruskamp FM. Policy options for cost containment of pharmaceuticals. Dukes MNG, Haaijer-Ruskamp FM, Joncheere CPde, Rietveld AH,

editors. Drugs and Money–Prices, affordability and cost containment., IOS Press, Amsterdam. 2003:29-54

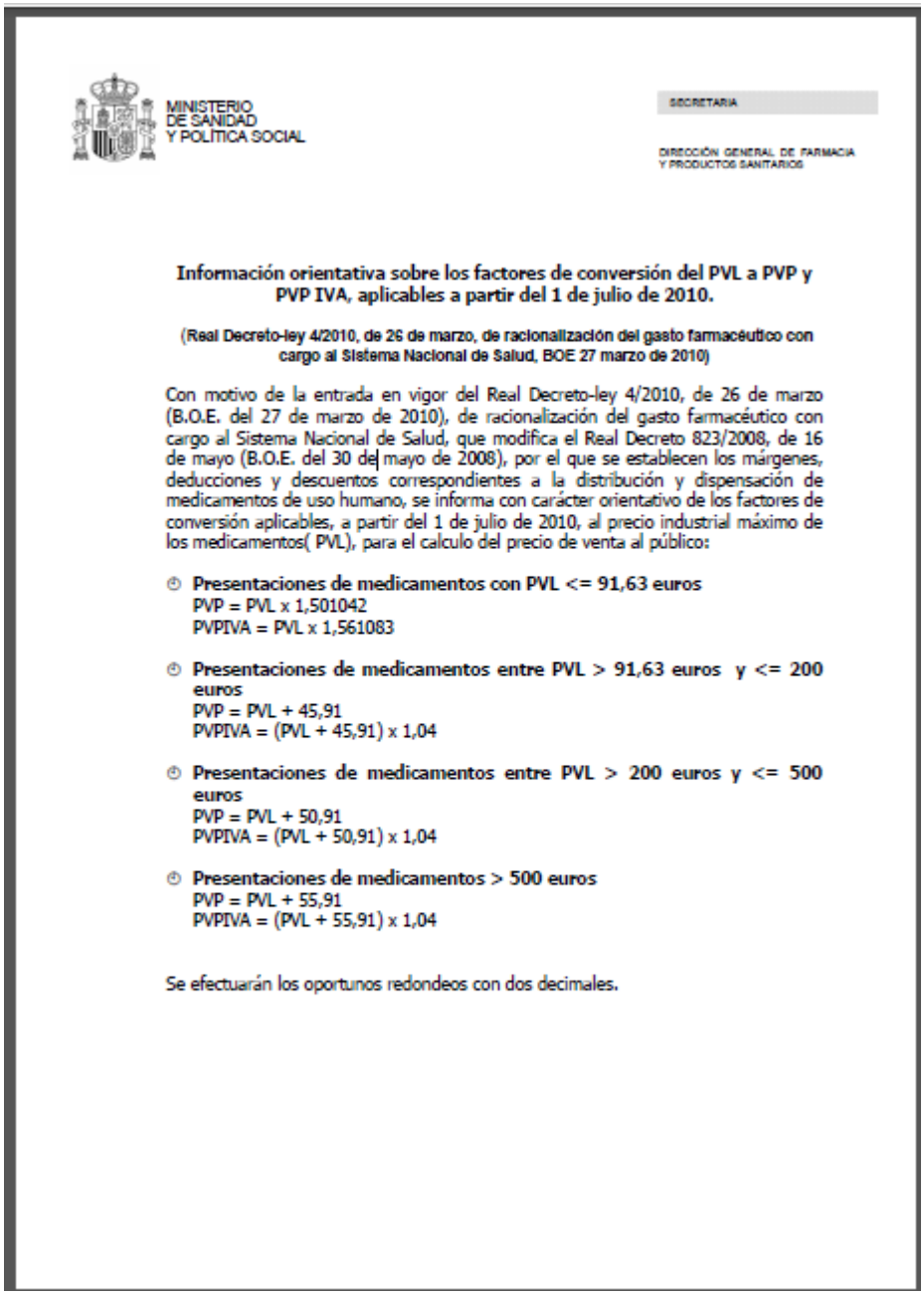
38. World Health Organisation. WHO guidelines on country pharmaceutical pricing policies. World Health Organization; 2015.
39. Mohamed O, Kreling DH. The Impact of a Pricing Policy Change on Retail Prices of Medicines in Egypt. Value in health regional issues. 2016 Sep 1;10:14-8.
40. Management Sciences for Health Financing and sustainability. Chapter 9 Pharmaceutical Pricing Policy. Available from: apps.who.int/medicinedocs/documents/s19585en/s19585en.pdf
41. Spinks J, Chen G, Donovan L. Does generic entry lower the prices paid for pharmaceuticals in Australia? A comparison before and after the introduction of the mandatory price-reduction policy. Australian Health Review. 2013 Nov 29;37(5):675-81.
42. Danzon PM, Kim JD. International price comparisons for pharmaceuticals. Pharmacoeconomics. 1998 Oct 1;14(1):115-28.
43. Hu J, Mossialos E. Pharmaceutical pricing and reimbursement in China: when the whole is less than the sum of its parts. Health Policy. 2016 May 1;120(5):519-34
44. Zareski R, Nestorovska AK, Grozdanova A, Dimitrova B, Suturkova LJ, Sterjev Z. The Effects of the New Methodology Application on the Method of Pricing of Drugs—The Case of the Republic of Macedonia. Value in health regional issues. 2016 Sep 1;10:19-28.
45. Law MR. Money left on the table: generic drug prices in Canada. Healthcare Policy. 2013 Feb;8(3):17.
46. Espin J, Rovira J, de Labry AO. WHO/HAI project on medicine prices and availability. Review series on pharmaceutical pricing policies and interventions. WHO Health Action Int. 2011 May.
47. Leopold C, Vogler S, Mantel-Teeuwisse AK, de Joncheere K, leufkens HG, Laing R. Differences in external price referencing in Europe – a descriptive overview. Health policy. 2012 Jan 1;1 04(1):50-60
48. Leopold C, Mantel-Teeuwisse AK, Seyfang L, Vogler S, de Joncheere K, Laing RO, Leufkens H. Impact of external price referencing on medicine prices – a price comparison among 14 European countries. Southern med review. 2012 Dec;5(2):34
49. Chen Y, Hu S, Dong P, Kornfeld Å, Jaros P, Yan J, Ma F, Toumi M. Drug Pricing Reform in China: analysis of piloted approaches and potential impact of the reform. Journal of market access & health policy. 2016 Jan 1;4(1):30458.

50. Anson A, Ramay B, de Esparza AR, Bero L. Availability, prices and affordability of the World Health Organization's essential medicines for children in Guatemala. Globalization and health. 2012 Dec;8(1):22.
51. Chahal HS, Fort NS, Bero L. Availability, prices and affordability of essential medicines in Haiti. Journal of global health. 2013 Dec;3(2).
52. Vogler S, Zimmermann N, de Joncheere K. Policy interventions related to medicines: Survey of measures taken in European countries during 2010-2015. Health Policy. 201 Dec 1; 120 (12):1363-77.
53. World Health Organization. Measuring medicine prices, availability, affordability and price components. Geneva: World Health Organization; 2008
54. Acosta A, Ciapponi A, Aaserud M, Vietto V, Austvoll-Dahlgren A, Kösters JP, Vacca C, Machado M, Diaz Ayala DH, Oxman AD. Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies. Cochrane Database Syst Rev. 2014 Jan 1;10(10).
55. Wirtz VJ, Santa-Ana-Tellez Y, Trout CH, Kaplan WA. Allocating scarce financial resources for HIV treatment: benchmarking prices of antiretroviral medicines in Latin America. Health policy and planning. 2012 Feb 24;27(8):638-48.
56. Vogler S, Kilpatrick K. Analysis of medicine prices in New Zealand and 16 European countries. Value in health. 2015 Jun 1;18(4):484-92.
57. Habl C, Schneider P, Németh G, Šebesta R. Euripid Guidance Document on External Reference Pricing (ERP).

ANNEXES

5.1 Annexure A

Spanish Ministry of Health – Published formula for the conversion of PVL to PVP



MINISTERIO
DE SANIDAD
Y POLÍTICA SOCIAL

SECRETARÍA

DIRECCIÓN GENERAL DE FARMACIA
Y PRODUCTOS SANITARIOS

Información orientativa sobre los factores de conversión del PVL a PVP y PVP IVA, aplicables a partir del 1 de julio de 2010.

(Real Decreto-ley 4/2010, de 26 de marzo, de racionalización del gasto farmacéutico con cargo al Sistema Nacional de Salud, BOE 27 marzo de 2010)

Con motivo de la entrada en vigor del Real Decreto-ley 4/2010, de 26 de marzo (B.O.E. del 27 de marzo de 2010), de racionalización del gasto farmacéutico con cargo al Sistema Nacional de Salud, que modifica el Real Decreto 823/2008, de 16 de mayo (B.O.E. del 30 de mayo de 2008), por el que se establecen los márgenes, deducciones y descuentos correspondientes a la distribución y dispensación de medicamentos de uso humano, se informa con carácter orientativo de los factores de conversión aplicables, a partir del 1 de julio de 2010, al precio industrial máximo de los medicamentos(PVL), para el calculo del precio de venta al público:

- **Presentaciones de medicamentos con PVL <= 91,63 euros**
  PVP = PVL x 1,501042
  PVPIVA = PVL x 1,561083

- **Presentaciones de medicamentos entre PVL > 91,63 euros y <= 200 euros**
  PVP = PVL + 45,91
  PVPIVA = (PVL + 45,91) x 1,04

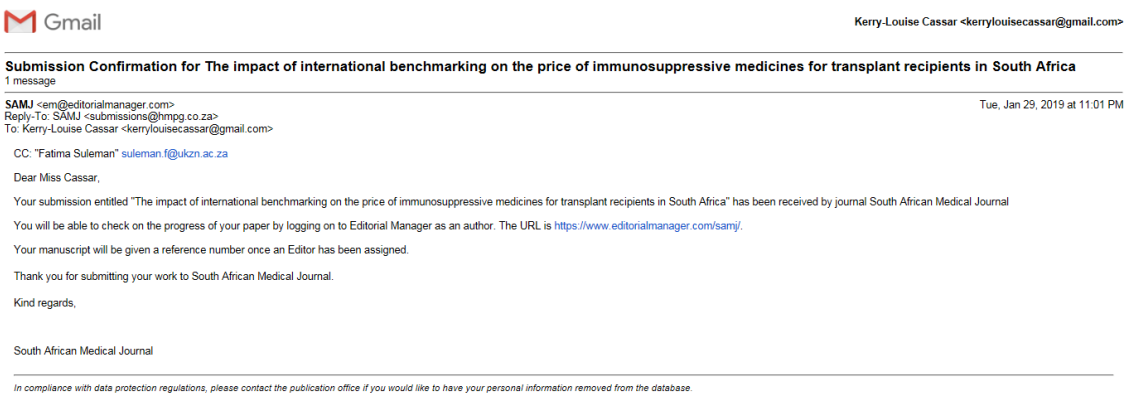
- **Presentaciones de medicamentos entre PVL > 200 euros y <= 500 euros**
  PVP = PVL + 50,91
  PVPIVA = (PVL + 50,91) x 1,04

- **Presentaciones de medicamentos > 500 euros**
  PVP = PVL + 55,91
  PVPIVA = (PVL + 55,91) x 1,04

Se efectuarán los oportunos redondeos con dos decimales.

5.2 Annexure B

Proof of submission to SAMJ



Gmail

Kerry-Louise Cassar <kerrylouisecassar@gmail.com>

Submission Confirmation for The impact of international benchmarking on the price of immunosuppressive medicines for transplant recipients in South Africa
1 message

SAMJ <em@editorialmanager.com>
Reply-To: SAMJ <submissions@hmpg.co.za>
To: Kerry-Louise Cassar <kerrylouisecassar@gmail.com>

Tue, Jan 29, 2019 at 11:01 PM

CC: "Fatima Suleman" suleman.f@ukzn.ac.za

Dear Miss Cassar,

Your submission entitled "The impact of international benchmarking on the price of immunosuppressive medicines for transplant recipients in South Africa" has been received by journal South African Medical Journal

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author. The URL is https://www.editorialmanager.com/samj/.

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to South African Medical Journal.

Kind regards,

South African Medical Journal

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.

5.3 Annexure C

Individual group comparisons per year – 2016, 2017 and 2018

Ciclosporin - Novartis Sandimmun 50mg/ml injection (1 vial)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	52.29	1.00	R 52.29
Australia	5.41	10.91	R 59.02
Canada	4.63	11.06	R 51.16
Brazil	14.96	4.22	R 63.14
Russia	77.06	0.22	R 16.95
South African state tender	26.40	1.00	R 26.40
Ciclosporin - Novartis Sandimmun 100mg/ml solution (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	64.16	1.00	R 64.16
New Zealand	3.96	10.23	R 40.54
Australia	6.32	10.91	R 68.91
Canada	5.03	11.06	R 55.61
Brazil	6.23	4.22	R 26.27
Russia	76.34	0.22	R 16.79
South African state tender	18.03	1.00	R 18.03
Ciclosporin - Novartis Sandimmun 100mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	61.65	1.00	R 61.65
New Zealand	3.56	10.23	R 36.38
Australia	5.43	10.91	R 59.19
Canada	5.66	11.06	R 62.56
Brazil	6.09	4.22	R 25.72
Russia	153.45	0.22	R 33.76
South African state tender	15.08	1.00	R 15.08
Ciclosporin - Novartis Neoral 25mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	15.66	1.00	R 15.66
New Zealand	0.89	10.23	R 9.13
Australia	1.28	10.91	R 13.96
Canada	1.45	11.06	R 16.04
Brazil	1.79	4.22	R 7.57
Russia	19.28	0.22	R 4.24
South African state tender	3.77	1.00	R 3.77
Mycophenolate mofetil - Roche Cellcept 500mg IV infusion (1 vial)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	196.38	1.00	R 196.38
Canada	32.00	11.06	R 353.92

Mycophenolate mofetil - Roche Cellcept 200mg/ml (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	11.52	1.00	R 11.52
New Zealand	1.13	10.23	R 11.61
Australia	1.48	10.91	R 16.17
Canada	1.85	11.06	R 20.50
South African state tender	7.17	1.00	R 7.17
Mycophenolate mofetil - Roche Cellcept 250mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	14.49	1.00	R 14.49
New Zealand	0.25	10.23	R 2.56
Australia	0.72	10.91	R 7.80
Canada	2.08	11.06	R 23.01
Russia	25.31	0.22	R 5.57
Mycophenolate mofetil - Sandoz 250mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	10.55	1.00	R 10.55
Australia	0.72	10.91	R 7.80
Canada	1.03	11.06	R 11.40
Russia	31.33	0.22	R 6.89
Mycophenolic acid - Novartis Myfortic 180mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	15.80	1.00	R 15.80
Australia	0.71	10.91	R 7.80
Canada	2.00	11.06	R 22.09
Brazil	6.17	4.22	R 26.04
Russia	75.86	0.22	R 16.69
South African state tender	3.60	1.00	R 3.60
Mycophenolic acid - Novartis Myfortic 360mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	31.60	1.00	R 31.60
Australia	1.43	10.91	R 15.60
Canada	4.00	11.06	R 44.19
Brazil	12.34	4.22	R 52.08
Russia	152.42	0.22	R 33.53
South African state tender	7.20	1.00	R 7.20
Mycophenolate mofetil - Roche 500mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	28.99	1.00	R 28.99
New Zealand	0.50	10.23	R 5.12
Australia	1.43	10.91	R 15.60

Canada	4.16	11.06	R 46.02
Brazil	10.55	4.22	R 44.52
Russia	47.64	0.22	R 10.48
Mycophenolate mofetil - Sandoz 500mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	15.79	1.00	R 15.79
Australia	1.43	10.91	R 15.60
Canada	2.06	11.06	R 22.81
Sirolimus - Pfizer Rapamune 1mg tablets			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	72.07	1.00	R 72.07
New Zealand	7.50	10.23	R 76.72
Australia	6.87	10.91	R 74.97
Canada	8.14	11.06	R 90.07
Brazil	23.88	4.22	R 100.76
Basiliximab - Novartis Simulect 20mg vial (1mg)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	2301.69	1.00	R 2 301.69
Brazil	4939.12	4.22	R 20 843.09
Russia	42871.17	0.22	R 9 431.66
Tacrolimus - Astellas Prograf 5mg/ml infusion (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	1137.52	1.00	R 1 137.52
Brazil	358.54	4.22	R 1 513.04
Russia	2311.91	0.22	R 508.62
Tacrolimus - Astellas Prograf 5mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	155.47	1.00	R 155.47
Australia	12.50	10.91	R 136.38
Australia	12.51	10.91	R 136.46
Canada	12.62	11.06	R 139.58
Brazil	36.47	4.22	R 153.91
Russia	721.12	0.22	R 158.65
South African state tender	81.51	1.00	R 81.51
Tacrolimus - Astellas Advagraf 5mg (1 capsule)			
South Africa	150.29	1.00	R 150.29
Australia	12.51	10.91	R 136.46
Canada	12.62	11.06	R 139.58
Russia	471.04	0.22	R 103.63
Tacrolimus - Astellas Prograf 1mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price

South Africa	32.15	1.00	R 32.15
Australia	2.50	10.91	R 27.29
Canada	2.52	11.06	R 27.87
Brazil	7.29	4.22	R 30.78
Brazil	7.29	4.22	R 30.78
Russia	142.24	0.22	R 31.29
South African state tender	16.47	1.00	R 16.47
Tacrolimus - Advagraf 1mg capsules (1 capsule)			
South Africa	30.89	1.00	R 30.89
Australia	2.50	10.91	R 27.29
Canada	2.52	11.06	R 27.87
Russia	94.18	0.22	R 20.72
Tacrolimus - Astellas Prograf 0.5mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	17.04	1.00	R 17.04
Australia	1.25	10.91	R 13.65
Canada	1.97	11.06	R 21.79
Russia	71.68	0.22	R 15.77
South African state tender	13.91	1.00	R 13.91
Tacrolimus - Astellas Advagraf 0.5mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	16.95	1.00	R 16.95
Australia	1.25	10.91	R 13.64
Canada	1.97	11.06	R 21.79
Russia	46.91	0.22	R 10.32
Everolimus - Novartis Certican 0.75mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	66.38	1.00	R 66.38
Australia	11.41	10.91	R 124.53
Brazil	23.84	4.22	R 100.61
Russia	195.02	0.22	R 42.90
South African state tender	30.21	1.00	R 30.21
Everolimus - Novartis Certican 0.25mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	22.13	1.00	R 22.13
Australia	3.80	10.91	R 41.51
Russia	69.11	0.22	R 15.20
South African state tender	10.07	1.00	R 10.07
Azathioprine - Aspen Imuran 50mg vial (1mg)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	603.57	1.00	R 603.57

New Zealand	126.00	10.23	R 1 288.98
Azathioprine - Aspen Imuran 50mg tablet (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	12.95	1.00	R 12.95
Australia	0.24	10.91	R 2.63
Canada	1.05	11.06	R 11.60
Brazil	2.22	4.22	R 9.37
Brazil	2.22	4.22	R 9.37
Azathioprine - Azamun 50mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	5.87	1.00	R 5.87
New Zealand	0.13	10.23	R 1.35
Australia	0.24	10.91	R 2.63
South African state tender	0.94	1.00	R 0.94
Equine gamma globulin - Pfizer Atgam 50mg/ml (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	1403.98	1.00	R 1 403.98
New Zealand	470.25	10.23	R 4 810.66

Table 3. Individual group comparisons – 2016 pricing

Ciclosporin -Novartis Sandimmun 50mg/ml ampoules 1ml			
Country	Unit price (1ml amp)	Conversion rate	ZAR unit price
South Africa	R 56.22	1.00	R 56.22
Australia	$5.41	10.20	R 55.18
Canada	$4.6260	10.25	R 47.43
Brazil	R$ 15.42	4.17	R 64.30
Russia	77.06 ₽	0.23	R 17.72
South African state tender	R 26.40	1.00	R 26.40
Ciclosporin - Novartis Neoral solution 100mg/ml 50ml (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 68.97	1.00	R 68.97
New Zealand	$3.96	9.46	R 37.49
Australia	$6.32	10.20	R 64.42
Canada	$5.0276	10.25	R 51.55
Brazil	R$ 6.42	4.17	R 26.76
Russia	76.34 ₽	0.23	R 17.56
South African state tender	R18.03	1.00	R 18.03
Ciclosporin - Novartis Neoral 100mg (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 66.27	1.00	R 66.27
New Zealand	$3.56	9.46	R 33.64

Australia	$4.55	10.20	R 46.44
Canada	$5.6560	10.25	R 57.99
Brazil	R$ 6.28	4.17	R 26.19
South African state tender	R 15.08	1.00	R 15.08
Russia	72.92 ₽	0.23	R 16.77
Ciclosporin - Sandoz 100mg (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 50.74	1.00	R 50.74
Australia	$4.55	10.20	R 46.44
Canada	$5.0900	10.25	R 52.19
Ciclosporin - Novartis Neoral 25mg (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 16.83	1.00	R 16.83
New Zealand	$0.89	9.46	R 8.44
Australia	$1.07	10.20	R 10.95
Canada	$1.4500	10.25	R 14.87
Brazil	R$ 1.85	4.17	R 7.71
Russia	19.28 ₽	0.23	R 4.44
South African state tender	R 3.77	1.00	R 3.77
Ciclosporin - Sandoz 25mg (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 12.92	1.00	R 12.92
Australia	$1.07	10.20	R 10.95
Canada	$1.3050	10.25	R 13.38
Mycophenolate mofetil - Roche Cellcept 500mg intravenous infusion (1 vial)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 211.11	1.00	R 211.11
Canada	$33.9025	10.25	R 347.60
Mycophenolate mofetil - Roche Cellcept 20mg/ml (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 12.39	1.00	R 12.39
New Zealand	$1.13	9.46	R 10.74
Australia	$1.48	10.20	R 15.12
Canada	$1.8536	10.25	R 19.00
South African state tender	R 7.17	1.00	R 7.17
Mycophenolate mofetil - Roche Cellcept 250mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 15.58	1.00	R 15.58
New Zealand	$0.25	9.46	R 2.37
Australia	$0.51	10.20	R 5.23
Canada	$2.0806	10.25	R 21.33

Russia	25.31 ₽	0.23	R 5.82
Mycophenolate mofetil - Sandoz 250mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 10.55	1.00	R 10.55
South Africa	R 7.69	1.00	R 7.69
Australia	$0.51	10.20	R 5.23
Canada	$1.0310	10.25	R 10.57
Russia	25.31 ₽	0.23	R 5.82
Mycophenolic acid - Novartis Myfortic 180mg (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 16.98	1.00	R 16.98
Australia	$0.71	10.20	R 7.29
Canada	$1.9977	10.25	R 20.48
Brazil	R$ 6.36	4.17	R 26.52
Russia	42.04 ₽	0.23	R 9.67
South African state tender	R 4	1.00	R 3.60
Mycophenolic acid - Novartis Myfortic 360mg (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 33.97	1.00	R 33.97
Australia	R 1.43	10.20	R 14.58
Canada	$3.9953	10.25	R 40.96
Brazil	R$ 12.72	4.17	R 53.04
Russia	86.39 ₽	0.23	R 19.87
Russia	110.48 ₽	0.23	R 25.41
South African state tender	R 7	0.23	R 1.66
Mycophenolate mofetil - Roche Cellcept 500mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 31.16	1.00	R 31.16
New Zealand	$0.50	9.46	R 4.73
Australia	$1.02	10.20	R 10.45
Canada	$4.1612	10.25	R 42.66
Brazil	R$ 13.05	4.17	R 54.40
Russia	47.64 ₽	0.23	R 10.96
Mycophenolate mofetil - Sandoz 500mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 15.79	1.00	R 15.79
Australia	$1.02	10.20	R 10.45
Canada	$2.0620	10.25	R 21.14
Sirolimus - Pfizer Rapamune 1mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 77.47	1.00	R 77.47

New Zealand	$7.50	9.46	R 70.95
Australia	$6.87	10.20	R 70.09
Canada	$8.2330	10.25	R 84.41
Brazil	R$ 24.61	4.17	R 102.61
Basiliximab - Simulect 20mg vial (1mg)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 2 474.32	1.00	R 2 474.32
Brazil	R$ 5 006.30	4.17	R 20 876.27
Russia	42 871.17 ₽	0.23	R 9 860.37
Tacrolimus - Prograf 5mg/ml IV infusion 5mgml (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 1 137.52	1.00	R 1 137.52
Brazil	R$ 363.42	4.17	R 1 515.45
Russia	2 311.91 ₽	0.23	R 531.74
Tacrolimus - Astellas Prograf 5mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 155.47	1.00	R 155.47
Australia	R 10.96	10.20	R 111.84
Canada	$12.6200	10.25	R 129.39
South African state tender	R 81.51	1.00	R 81.51
Brazil	R 36.97	4.17	R 154.16
Russia	256.36 ₽	0.23	R 58.96
Tacrolimus - Astellas Advagraf 5mg (1 capsules)			
South Africa	R 161.56	1.00	R 161.56
Australia	R 12.51	10.20	R 127.57
Canada	$12.6200	10.25	R 129.39
Russia	301.71 ₽	0.23	R 69.39
Tacrolimus - Astellas Prograf 1mg capsule (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 32.15	1.00	R 32.15
Australia	$2.19	10.20	R 22.38
Australia	$2.19	10.20	R 22.38
Canada	$2.5200	10.25	R 25.84
South African state tender	R 16.47	1.00	R 16.47
Brazil	R$ 7.39	4.17	R 30.83
Brazil	R$ 7.39	4.17	R 30.83
Russia	51.78 ₽	0.23	R 11.91
Tacrolimus - Astellas Advagraf 1mg capsule (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 33.20	1.00	R 33.20
Australia	$2.19	10.20	R 22.38

Canada	$2.5200	10.25	R 25.84
Russia	73.70 ₽	0.23	R 16.95
Tacrolimus - Astellas Prograf 0,5mg capsule (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 17.04	1.00	R 17.04
Australia	$1.10	10.20	R 11.19
Australia	$1.25	10.20	R 12.76
Canada	$1.9700	10.25	R 20.20
Russia	25.89 ₽	0.23	R 5.96
South African state tender	R 13.91	1.00	R 13.91
Tacrolimus - Astellas Advagraf 0,5mg capsule (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 18.22	1.00	R 18.22
Australia	R 1.25	10.20	R 12.76
Canada	$1.9700	10.25	R 20.20
Russia	28.15 ₽	0.23	R 6.47
Everolimus - Novartis Certican 0.75mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 71.36	1.00	R 71.36
Australia	$11.41	10.20	R 116.43
Brazil	R$ 24.57	4.17	R 102.46
Russia	195.02 ₽	0.23	R 44.85
South African state tender	R 30.21	1.00	R 30.21
Everolimus - Novartis Certican 0.25mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 23.79	1.00	R 23.79
Australia	$3.80	10.20	R 38.81
Russia	69.11 ₽	0.23	R 15.89
South African state tender	R 10.07	1.00	R 10.07
Azathioprine - Aspen Imuran 50mg injection (vial)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 648.84	1.00	R 648.84
New Zealand	$60.00	9.46	R 567.60
Canada	$101.34	10.25	R 1 039.03
Azathioprine - Aspen Imuran 50mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 13.92	1.00	R 13.92
Australia	$0.19	10.20	R 1.96
Canada	$1.0540	10.25	R 10.81
Brazil	R$ 2.29	4.17	R 9.54
Brazil	R$ 2.29	4.17	R 9.54

Azathioprine - Azamun 50mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 6.31	1.00	R 6.31
New Zealand	$0.11	9.46	R 1.00
Australia	$0.19	10.20	R 1.96
South African state tender	$0.94	1.00	R 0.94
Equine gamma globlin - Pfizer Atgam 50mg/ml ampoule (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 1 509.24	1.00	R 1 509.24
New Zealand	$470.25	9.46	R 4 448.57

Table 4. Individual group comparisons - 2017 pricing

Ciclosporin -Novartis Sandimmun 50mg/ml ampoules 1ml			
Country	Unit price (1ml amp)	Conversion rate	ZAR unit price
South Africa	R 56.92	1	R 56.92
Australia	$5.41	9.93	R 53.71
Canada	$4.6260	10.06	R 46.54
Brazil	R$ 15.42	3.91	R 60.23
Russia	77.06 ₽	0.22	R 16.81
South African state tender	R 26.40	1.00	R 26.40
Ciclosporin - Novartis Sandimmun 100mg/ml oral solution 50ml			
Country	Unit price (1ml)	Conversion rate	ZAR unit price
South Africa	R 69.84	1.00	R 69.84
New Zealand	$3.96	9.18	R 36.38
Australia	$6.32	9.93	R 62.72
Canada	$5.1130	10.06	R 51.44
Brazil	R$ 6.42	3.91	R 25.09
Russia	R$ 76.34	0.22	R 16.79
South African state tender	R$ 18.03	1.00	R 18.03
Ciclosporin - Novartis Neoral 100mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 67.10	1.00	R 67.10
New Zealand	R 3.56	9.18	R 32.65
Australia	R 4.55	9.93	R 45.21
Canada	$5.7740	10.06	R 58.09
Brazil	R$ 6.28	3.91	R 24.56
Russia	72.92 ₽	0.22	R 16.04
South African state tender	R$ 15.08	1.00	R 15.08
Ciclosporin - Sandoz Ciclohexal 100mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 51.38	1.00	R 51.38

Australia	$4.55	9.93	R 45.20
Canada	$5.0900	10.06	R 51.21
Ciclosporin - Novartis Neoral 25mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 17.04	1.00	R 17.04
New Zealand	R 0.89	9.18	R 8.19
Australia	R 1.07	9.93	R 10.66
Canada	$1.4800	10.06	R 14.89
Brazil	R$ 1.85	3.91	R 7.22
Russia	19.28 ₽	0.22	R 4.24
South African state tender	R 3.77	1.00	R 3.77
Ciclosporin - Sandoz Ciclohexal 25mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 13.08	1.00	R 13.08
Australia	R 1.07	9.93	R 10.66
Canada	$1.3050	10.06	R 13.13
Mycophenolate mofetil - Roche Cellcept 500mg intravenous infusion (1 vial)			
Country	Unit price (1 vial)	Conversion rate	ZAR unit price
South Africa	R 213.77	1.00	R 213.77
Canada	$33.9025	10.06	R 341.06
Mycophenolate mofetil - Roche Cellcept 200mg/ml oral suspension (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 12.54	1.00	R 12.54
New Zealand	R 1.13	9.18	R 10.41
Australia	R 1.48	9.93	R 14.71
Canada	$1.8536	10.06	R 18.65
South African state tender	$7.1702	1.00	R 7.17
Mycophenolate mofetil - Cellcept 250mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 15.78	1.00	R 15.78
New Zealand	$0.25	9.18	R 2.29
Australia	$0.44	9.93	R 4.37
Canada	$2.0806	10.06	R 20.93
Russia	25.31 ₽	0.22	R 5.57
Mycophenolic acid - Novartis Myfortic 180mg enteric coated tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 17.20	1.00	R 17.20
Canada	$1.9977	10.06	R 20.10
Australia	$0.71	9.93	R 7.10
Brazil	$6.36	3.91	R 24.84
Russia	$42.04	0.22	R 9.25

South African state tender	$3.60	1.00	R 3.60
Mycophenolic acid - Novartis Myfortic 360mg enteric coated tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 34.39	1.00	R 34.39
Australia	$1.43	9.93	R 14.19
Canada	$3.9953	10.06	R 40.19
Brazil	R$ 12.72	3.91	R 49.68
Russia	R$ 86.39	0.22	R 19.01
South African state tender	R$ 7.20	1.00	R 7.20
Mycophenolate mofetil - Roche Cellcept 500mg Tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 31.56	1.00	R 31.56
New Zealand	$0.50	9.18	R 4.59
Australia	$0.88	9.93	R 8.73
Canada	$4.1612	10.06	R 41.86
Brazil	R$ 13.05	3.91	R 50.96
Mycophenolate mofetil - Sandoz mycophenolate 500mg Tablets (1 tablet)			
South Africa	R 15.99	1.00	R 15.99
Australia	$0.88	9.93	R 8.73
Canada	$2.0620	10.06	R 20.74
Spain	0.97 €	15.25	R 14.77
Mycophenolate mofetil - Sandoz 250mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 10.68	1.00	R 10.68
South Africa	R 7.78	1.00	R 7.78
Australia	$0.44	9.93	R 4.37
Canada	$1.0310	10.06	R 10.37
Spain	0.48 €	15.25	R 7.39
Russia	25.31 ₽	0.22	R 5.57
Sirolimus - Pfizer Rapamune 1mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 78.45	1.00	R 78.45
New Zealand	R 7.50	9.18	R 68.82
Australia	R 6.87	9.93	R 68.21
Canada	$8.3483	10.06	R 83.98
Spain	3.60 €	15.25	R 54.83
Brazil	R$ 24.61	3.91	R 96.11
South African state tender	55.66 €	1.00	R 55.66
Basiliximab - Novartis Simulect 20mg vial for injection (1 vial)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 2 505.49	1.00	R 2 505.49

Brazil	R$ 5 006.30	3.91	R 19 554.39
Russia	42 871.17 ₽	0.22	R 9 431.66
Tacrolimus - Prograf 5mg/ml 1m injection (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 1 137.52	1.00	R 1 137.52
Brazil	R$ 363.42	3.91	R 1 419.49
Russia	2 311.91 ₽	0.22	R 508.62
Tacrolimus - Astellas Prograf 5mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 155.47	1.00	R 155.47
Australia	$10.96	9.93	R 108.84
Canada	$12.6200	10.06	R 126.96
Russia	256.36 ₽	0.22	R 56.40
South African state tender	R 81.51	1.00	R 81.51
Tacrolimus - Astellas Advagraf XL 5mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 161.56	1.00	R 161.56
Australia	R 12.51	9.93	R 124.16
Canada	$12.6200	10.06	R 126.96
Russia	301.71 ₽	0.22	R 66.38
Tacrolimus - Astellas Prograf 1mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 32.15	1.00	R 32.15
Australia	$2.19	9.93	R 21.78
Canada	$2.5200	10.06	R 25.35
Russia	51.78 ₽	0.22	R 11.39
South African state tender	R 16.47	1.00	R 16.47
Tacrolimus - Astellas Advagraf XL 1mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 33.20	1.00	R 33.20
Australia	$2.19	9.93	R 21.78
Canada	$2.5200	10.06	R 25.35
Russia	73.70 ₽	0.22	R 16.22
Tacrolimus - Astellas Prograf 0.5mg capsules (1 capsule)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 17.04	1.00	R 17.04
Australia	$1.10	9.93	R 10.89
Canada	$1.9700	10.06	R 19.82
Russia	25.89 ₽	0.22	R 5.70
South African state tender	R 13.91	1.00	R 13.91
Tacrolimus - Astellas Advagraf XL 0.5mg capsules (1 capsule)			

Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 18.22	1.00	R 18.22
Australia	$1.25	9.93	R 12.42
Canada	$1.9700	10.06	R 19.82
Russia	28.15 ₽	0.22	R 6.19
Everolimus - Novartis Certican 0.75mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 72.26	1.00	R 72.26
Australia	$11.41	9.93	R 113.31
Spain	4.97 €	15.25	R 75.72
Brazil	R$ 24.57	3.91	R 95.97
Russia	195.02 ₽	0.22	R 42.90
South African state tender	R 30.21	1.00	R 30.21
Everolimus - Novartis Certican 0.25mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 24.09	1.00	R 24.09
Australia	$3.80	9.93	R 37.77
Spain	1.66 €	15.25	R 25.24
Russia	69.11 ₽	0.22	R 15.20
South African state tender	R 10.07	1.00	R 10.07
Azathioprine - Aspen Imuran 50mg injection (1 vial)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 657.01	1.00	R 657.01
New Zealand	$60.00	9.18	R 550.53
Canada	$101.3400	10.06	R 1 019.48
Azathioprine - Aspen Imuran 50mg tablets (1 tablet)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 14.10	1.00	R 14.10
New Zealand	$0.11	9.18	R 0.97
Australia	$0.19	9.93	R 1.91
Canada	$1.0686	10.06	R 10.75
Brazil	R$ 2.29	3.91	R 8.94
Brazil	R$ 2.29	3.91	R 8.94
Equine gamma globulin - Pfizer Atgam 50mg/ml ampoule (1ml)			
Country	Unit price	Conversion rate	ZAR unit price
South Africa	R 1 528.25	1.00	R 1 528.25
New Zealand	$470.25	9.18	R 4 314.81

Table 5. Individual group comparisons - 2018 pricing