

RESEARCH PROJECT

**TITLE: INNOVATOR MEDICINES VERSUS GENERIC MEDICINE PACKAGE
INSERTS SAFETY AMENDMENTS, THE REALITY IN SOUTH AFRICA.**

BY

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ABSTRACT

Introduction

Availability of clinically relevant and unbiased medicine information goes a long way in promoting rational use of medicines. The package insert (PI) is one of the sources of information utilised by healthcare professionals for accessing relevant medicine information such as indications, contra-indications and special precautions (Singh, Mohan, Kumar, & Gupta,2016). It is important that the PI contains updated safety information. The safety information in the PIs of the innovator and generic medicines are expected to be the similar since they contain the same active ingredients. Generic medicines have the same efficacy and safety as innovator medicines and are considered bioequivalent. Generic medicines are interchangeable with innovator medicines.

Purpose

1. To determine whether the package inserts of generic medicines contained the same safety information as those of innovator medicines.
2. To assess the process of medicine package insert amendments.

Method

Statins and anti-hypertensives were chosen for data collection since they are some of the most-used medicines because of increased prevalence of cholesterolaemia and hypertension. Many statin generic equivalents are also available on the South African market (Truter,2014). Twenty-five package inserts of registered statins and anti-hypertensive medicines were examined. The package inserts of generics were compared with those of innovator medicines. These package inserts were of products containing the following active ingredients: simvastatin, rosuvastatin, artovastatin, enalapril maleate, amlodipine, nifedipine and irbesartan. The process of medicine package insert amendments was assessed.

Results/Conclusion

The package inserts for innovator and generic medicines differed in information content at some sections. The information in innovator medicines PIs was not similar to those of generic ones in 34% of those examined, while in 66% the information was similar.

DECLARATION

I declare that this thesis that I now submit for assessment on the program of study leading to the award of MSc Pharmacy Administration and Policy Regulation has not been submitted as an exercise for a degree at this or any other institution. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work.

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Signed.....

..... **Dated**



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ABBREVIATIONS

MCC-Medicines Control Council

FDA- Food and Drugs Administration

PI(s)- Package Insert (s)

PIL(s) - Patient Information Leaflet(s)

S.A. - South Africa

NDP- National Drug Policy

CVD- Cardiovascular Disease

ICH- International Conference of Harmonisation

SPI- Standardised Package Insert

SRPINS-Safety Related Package Insert Notifications

EMA- European Medicines Agency

CTD-Common Technical Document

UK- United Kingdom

UK SPC- United Kingdom Summary of Product Characteristics

WHO-World Health Organization

BBWs-Black Box Warnings

CC-Clinical Committee

CCR-Clinical Committee Recommendations

CCDS-Company Core Data Sheet

PIC/S-Pharmaceutical Inspection Co-operation Scheme

Interchangeable words

Innovator products; innovator medicines; brand medicines; reference medicines

Generic products; generic medicines; multi-source medicines Medicines Control Council; Council; regulator



TABLE OF CONTENTS

Title Page.....	1
Abstract.....	2
Declaration	3
Acknowledgements.....	4
Abbreviations.....	5
Table of Contents	6

INNOVATOR MEDICINES VERSUS GENERIC MEDICINE PACKAGE**INSERT SAFETY AMENDMENTS, THE REALITY IN SOUTH AFRICA**

Chapter 1: Introduction.....	7-9
Chapter 2: Literature review	
2.1 Package inserts amendments in South Africa.....	10-14
2.2 Package inserts with different content.....	14-16
2.3 Package inserts in other countries.....	17
Chapter 3: Methodology.....	18
Chapter 4: Findings and Analysis/Discussion.....	19-33
Chapter 5: Conclusion and Recommendations	
5.1 Conclusion.....	34
5.2 Recommendations	34-36
Bibliography.....	37-39
Appendices	
Appendix 1: Research proposal.....	40-44

INNOVATOR MEDICINES VERSUS GENERIC MEDICINE PACKAGE INSERT SAFETY AMENDMENTS, THE REALITY IN SOUTH AFRICA

CHAPTER 1: INTRODUCTION

A package insert (PI) is regarded as the document that ensures the safe and effective use of the medicine under most circumstances. It presents a scientifically objective account of the use and limitation of medicines as established by the supporting evidence (PI guideline, 2014). The Medicines Control Council (MCC) approves the PI as part of the process of registration of medicines. The Medicines Control Council (Hereinafter called “The Council”) is a national regulatory authority that ensures all registered medicines in South Africa are of the required quality, safety and efficacy. The members of the Council are appointed by the National Minister of Health. The Council is supported by nine active technical committees (expert committees), these committees make recommendations to them. The Council makes final decisions or passes the necessary resolutions to approve the registrations of medicines and to approve package insert amendments.

The various committees of the MCC (“The Council”) are:

Pharmaceutical and Analytical Committee

Complementary Medicines Committee

Clinical Committee

Biological Medicines Committee

Names and Scheduling Committee

Clinical Trials Committee

Veterinary Clinical Committee

Legal Committee

Pharmacovigilance Committee

The Clinical Committee (CC) is responsible for the evaluation of package inserts.

Registration of medicines in South Africa is governed by the Medicines and Related Substances Control Act 101 of 1965 as amended and the Regulations and Guidelines published in terms thereof. Regulations 9 of Act 101 of 1965 as amended provide information on the format and content of the package insert. The South African PI guideline has details about the headings of package insert and how information should

be presented under each of these. This guideline is intended to assist applicants with the compilation of the PI for medicines registration and post-registration amendments (package insert guideline, 2014)

One of the objectives of the PI guideline is to enhance consistency in the content of package inserts which is the main reason for this study i.e. to investigate whether there is consistency between package inserts of innovator and generic medicines.

The main headings of the package insert are listed below:

- Scheduling status
- Proprietary name and Dosage form
- Composition
- Pharmacological classification
- Pharmacological Action
- Pharmacodynamic properties
- Pharmacokinetic properties
- Indications
- Contra-indications
- Warnings and Special Precautions
- Interactions
- Pregnancy and Lactation
- Dosage and Directions for use
- Side-effects
- Known Symptoms of Overdosage and Particulars of its Treatment
- Identification
- Presentation
- Storage instructions
- Registration number
- Name and business address of the holder of the certificate of registration
- Date of publication of the package insert



The purpose of this study was focused on the headings that fall under clinical evaluations of the package inserts. These are pharmacological action, indications, contra-indications, warnings and special precautions, interactions, pregnancy and lactation, dosage and directions for use, side-effects, and known symptoms of overdosage and particulars of its treatment.

Medical practitioners, pharmacists and other healthcare professionals are guided by the package insert document for the safe use of registered medicines. Packaging of registered medicines must include approved PIs for both branded and generic products as well as patient information leaflets (PILs). A PIL should be patient-friendly and should

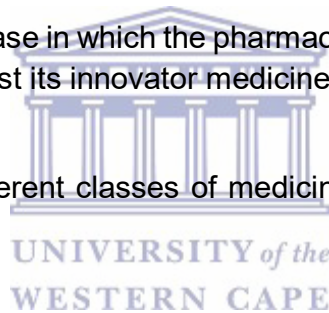
include lay terminology and be directed at the patient, while a PI uses medical terms understood by healthcare professionals.

The aim of the study was to determine whether package inserts of generic and branded medicines are the same and to look at the process of package insert amendments. The package inserts of innovator and generic medicines will be evaluated to examine whether safety information were the same and were consistent with each other. This is important since generic and innovator medicines contain the same active ingredients and are therapeutic equivalents.

Generic medicine PIs are compared with those of innovator ones as the latter were the first to be approved by MCC with the registration of the new chemical entity medicines. These PIs therefore serve as a benchmark as they are expected to contain complete information and data on a specific medicine, as manufacturers are required to submit clinical study information for registration. In the case of generic applications, only bioequivalence data is needed for registration.

This study was prompted by a case in which the pharmacodynamic properties of a generic medicine PI was checked against its innovator medicine PI and found to contain different information in the PI.

In this study the PIs of two different classes of medicines were considered, viz. statins and anti-hypertensives.



CHAPTER 2: LITERATURE REVIEW

2.1. Package insert amendments in South Africa

The MCC approves PI as part of the medicines registration process for generic and innovator medicines. Generic medicine as defined by the World Health Organization (WHO) is a pharmaceutical product usually intended to be interchangeable with an innovator product and manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusive rights. Generic medicines contain the same active ingredient(s) as the innovator medicines and equivalence is confirmed through bioavailability/bioequivalent studies before registration. Generic medicines are regarded as copies of innovator medicines and are therefore expected to have the same safety and efficacy profiles.

Innovator/branded/reference medicines contain a new chemical entity (a new molecule) to be registered by the regulatory authority. To register this type of medicine, information about pre-clinical and clinical trials should be provided to prove safety and efficacy for the required indication and population at the required specified dose. A medicine registered in another country is still considered a new chemical entity and is considered an innovator medicine if it is registered in South Africa for the first time. Innovator medicines are also used as references for the registration of generic medicines. According to the Pharmaceutical and Analytical guideline (2011, p 8) products containing chemical entities/active moieties not registered in South Africa cannot be used as reference products in efficacy and safety studies submitted in support of an application. An innovator product registered by the council (MCC) and procured in South Africa can be considered as a reference product. Innovator medicines have exclusivity to be marketed without competition from generic medicines for 20 years after registration. This patent protection can be extended to medicine indications also.

The PIs of the innovator medicines will be compared with generic medicines PIs since innovator medicines are also used as references during registration of generic medicines.

The use of generic medicines has increased. According to the Medicor Medicine Review (2014) an increase in use has been noted in South Africa from 53.4% in 2012 to 54.5% in 2013. The use of generic medicines in South Africa was promoted by the establishment of the National Drug Policy (NDP) which aims to increase access to and affordability of essential medicines to all South Africans. The NDP states that the government should ensure an adequate and reliable supply of safe and cost-effective medicines of acceptable quality to all citizens of South Africa and to promote the rational use of medicines by prescribers, dispensers and consumers (NAPM, 2009).

Innovator medicines can be substituted by generic medicines in South Africa as stated under section 22F of the Medicines and Related Substance Control Act 101 of 1965 as

amended. Generic substitution was introduced in South Africa in the early 2000 and the intervention resulted in an increase in the use of generic medicines and an average decrease in the price of medicines (Patel, Gauld, Norris and Rades, 2009).

It was found that after patent expiry, more innovator medicines are being switched to generic equivalents and the claims for innovator medicines have decreased from 23 percent in 2005 to 17 percent in 2007 (NAPM,2009). With an increased use of generic medicines, it is necessary that all information contained in innovator medicine package inserts be included in the generic ones and that healthcare professionals get detailed and consistent information about the medicines they prescribe. This should include the safety profile and risks and how such risks should be minimised or prevented and the correct use of medicines.

A ministerial task team (2008) found that the number of generic applications increased from 508 in 2003 to 801 in 2006. To register a generic medicine in South Africa, the most recently approved innovator package insert should be used as one of the references for the compilation of generic package insert. The indications, dosage and directions for use and the safety profile of the generic medicine should at least be in line with the innovator medicine package insert (PI guidelines, 2014, p 4). According to the South African PI guideline, applicants should ensure that all safety aspects are updated in line with the latest editions of the acceptable references. Source references which may be acceptable include (PI guideline, 2014):

- Goodman and Gilman: The pharmacological basis for therapeutics
- Martindale: The Complete Drug Reference
- USP (United states pharmacopeia): Dispensing information
- MCC: monographs for 'old medicines'
- Other references or peer-reviewed updated references, including information obtained from other regulatory authorities with which the council aligns itself. These are:

1. a member of the International Conference of Harmonisation (ICH) i.e. USA (FDA), European Union (EMA and National Regulatory Authorities) and Japan, ICH observer, i.e. Switzerland (Swissmedic) and Canada (Health Canada);
2. a regulatory authority associated with an ICH regulatory authority member through a legally binding mutual recognition agreement i.e. Australia, Norway, Iceland and Liechtenstein;
3. a member of PIC/S (Pharmaceutical Inspection Co-operation Scheme) for quality matters relating to good manufacturing practice.

Once a medicine has been registered, a pharmaceutical company may change (amendments/safety updates) the PIs of registered medicines for a number of reasons.

Package insert amendment or labeling update is required whenever important safety information becomes available during post-marketing surveillance. This can be information from periodic safety update reports (PSURs), to report an overview of worldwide safety experiences, summarise safety data within a specified period and provide evaluation of the benefit/risk of the product (Saville, Bushe, 2012).

The two areas for changes are pharmaceutical aspects of the product (quality control, manufacturing, shelf-life, etc.) and clinical aspects of the product. In this study attention will be paid to the clinical part of the amendment.

For the package insert to be amended or changed after registration, its approved package insert, a proposed amended package insert and evidence/motivation for the change should be submitted together with the notification of package insert amendment form (PI guideline, 2014). The package insert amendments can affect the content under any heading of the package insert; it can affect the pharmacological action, indications, contra-indications, warnings and special precautions, interactions, pregnancy and lactation, dosage and direction for use, side-effects and known symptoms of overdose and particulars of its treatment. Details of each section of the PI are explained below:

Pharmacological action

Pharmacological action describes the pharmacodynamic and pharmacokinetic properties of the medicines. Pharmacodynamic properties describe the mechanism of action of the medicines, pharmacodynamic effects and relevant clinical efficacy, while pharmacokinetic properties describe the absorption, distribution, protein binding, biotransformation, and elimination of the active substance(s) (PI guideline, 2014)

Indications

Indications describe the use of medicine as proven by the clinical studies; it defines the target disease. distinguishing between treatment, primary prevention, secondary prevention and diagnostic indications (PI guideline, 2014)

Contra-indications

Contra-indications describe instances where medicines should not be used; this could include particular clinical diagnoses, concomitant diseases, demographic factors (e.g. gender, age or predisposition) (e.g. metabolic or immunological factors, prior adverse reaction to the medicine or class of medicines) where the use of a medicine may be life-threatening or cause mortality or serious morbidity (PI guideline, 2014). Contra-indications in a package insert provides the strongest safety-based guidance for the health care practitioner (Garbe, 2006)

Warnings and special precautions

This section of the PI warns the healthcare professionals about the risk of the medicine, precautions to be taken to avoid or minimise such risk, and conditions under which use of medicine could be acceptable provided that special conditions for use are fulfilled.

Interactions

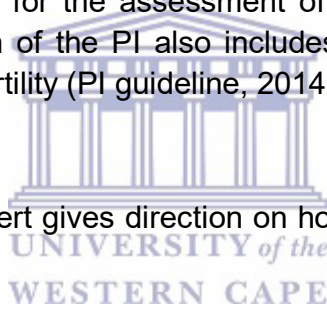
This section is about information on interactions with other medicines and food that can affect the effectiveness of the medicine. Details are stated on whether the use of medicine could be contra-indicated or the dose reduced if plasma levels of the active ingredient are increased or reduced with the use of other medicines.

Pregnancy and lactation

In this section, information about the use of medicine during pregnancy and lactation is stated as well as acts on human experience and conclusion from preclinical toxicity studies which are of relevance for the assessment of risks associated with exposure during pregnancy. This Section of the PI also includes the effect of use in women of childbearing potential and on fertility (PI guideline, 2014)

Dosage and direction for use

This section of the package insert gives direction on how the medicine should be used, and the duration of such use.



Side-effects

This section should contain information of side-effects (adverse reactions) from clinical trials, post-marketing studies, or spontaneous reports attributed to the medicine (PI guideline, 2014).

Known symptoms of overdose and particulars of its treatment

This section contains acute symptoms and signs of overdose and also include recommended management of overdose e.g. symptomatic treatment, or in relation to specific agonists/antagonists or methods to increase elimination of the medicines e.g. dialysis (PI guideline, 2014).

Safety updates in both innovator and generic medicines informs a prescriber of the possible risks associated with the use of these medicines and how to avoid the risks if possible. Package insert updates are basic tools to communicate new safety information to healthcare professionals, and this process should be done as soon as possible. The

FDA describes the communication of risks and benefits as “the cornerstone of risk management efforts for prescription drugs” (Garbe, 2006, p 87). The benefit/risk ratio should be assessed during evaluations of package inserts amendments. Some of the safety information obtained after a product has been registered can shift the benefit/risk ratio of the product resulting in withdrawal of the product from the market.

2.2. Package inserts with different content

According to WHO (WHO/DMP/RGS/98.5), an amendment for a change for use in an approved product (e.g. indication or patient population) would make the product not interchangeable with other brands and hence would not be acceptable unless the product information of all other brands were changed in the same way. It is normally not acceptable to have two equivalent multisource medicines (generics) on the same market with product information that does not match. One or both sets of product information will have to be amended so that they are consistent, although the wording need not be identical. Differences in medicine product information may have to be tolerated where local legislation allows new uses to be patented (e.g. new indication in the case of pharmaceuticals) or where market exclusivity arrangements apply.

When the indications for an innovator medicine is patented, the generic manufacturer will only be able to add the indication that is not restricted, but now with the substitution legislation, innovator medicines in the market may be substituted by less expensive generic medicines. If the generic medicine does not have some of the indications because of patent restriction, then some of these products may be used off-label by the prescriber or substituted when dispensed in a pharmacy. This is a grey area that needs further exploring.

Differences in medicine information can also be experienced with medicines of the same class, for example differences in black box warnings (BBWs) of medicines in the same class. Black box warnings are the most important medication-related warnings that can be placed in the package insert and highlight major medicine-related risks, but some of the medicines did not even have BBWs like other medicines in the same class (Panagiotou, 2011,p 603).These differences can have major implications during medicines use and can put the patients using the medicines in danger of being harmed if the labeling is not updated accordingly and the patient made aware of the risks associated with the use of a specific medicine.

The differences in the package inserts information was also stated in (Hisashi, 2004) when the innovator/generic medicine point average was calculated for each item of information. A large difference in information quantity was observed in those items of information such as “Therapeutic use”, “Safety” or “Side-effects”. This result suggests that information on generics that did not fall within one of these categories was based on the

information available for the innovator products. The result (Hisashi, 2004) suggests that the information on generics need not be evaluated from a standpoint of generic medicines in general, but in terms of individual drug markers. Availability of information varies from marker to marker.

Generic medicines contain the same active ingredient(s) as innovator medicines but different excipients. If there are specific excipients that patients can react to, it should be stated in the package insert under warnings. This can result in package inserts that contain different safety information. For example, allergic reactions were reported with the inclusion of crosscarmellose sodium used as an excipient in generic furosemide in a patient who previously took innovator furosemide without experiencing this. The same can happen with two products of the same molecule in which one contains lactose in its formulation. The patient with lactose intolerance may experience gastrointestinal disturbances if switched to the product with lactose-based excipient, which could affect gut transport time and overall medicine absorption, thus affecting systemic levels of the medicine (Dunne, Shannon, Dunne, & Cullen, 2013. p 11). Prescribers should be aware of this when substituting an equivalent. This should be clearly stated in the PI.

Medicines with the same active, innovator and generics, and also between generics can present different information in the package inserts. A study conducted in UK identified highly varying contra-indications among different methylphenidate formulations. The reason for such variation was not clear, according to the study, but may have resulted from different companies submitting separate PSURs for their respective methylphenidate-containing medicines (Suville & Bushe, 2012). This would cause confusion to the prescribers and even other healthcare professionals; patients can receive medicines while having conditions that are contra-indicated because some of the contra-indications are not reflected in the package insert. It can also create a wrong perception that even when medicines are equivalent, either a generic or an innovator is better or safer than the other one because it did not contain some contra-indications.

Differences in the package inserts of innovator and generic medicine information may cause a problem for the consumers who may have a perception that generic medicines are not of good quality. Although government promotes the use of generic medicines, some consumers have poor perceptions about generic medicines and why they are cheaper. They consider generic medicines supplied free of cost by the state as of poor quality and such medicines were treated with suspicion (Patel, Gault, Norris & Rades, 2009). When the package inserts of generic medicines have less or more side-effects than innovator medicines then the quality of generics may become suspect. The perceptions that generic medicines are less safe and effective than the innovator medicines are considered to be unfounded; a review and meta-analysis looking at the clinical equivalence of generics and brand name medicines used in cardiovascular

disease showed no superiority of the originator medicine over the generic medicine (Sheppard, 2009).

The FDA according to the Hatch-Waxman Act of 1984 requires the labeling for a generic to be the same as the labeling already approved for innovator medicine from which it was copied. Hatchman-Waxman's Abbreviated New Drug Application Process linked efficacy, safety and harm to the information in the innovator medicine label. As a result, innovator manufacturers became the steward for the public warning for all generic medicines. The problem arises in case the innovator manufacturer stops manufacturing the innovator product after the introduction of the generic products, leaving a gap in responsibility for such labeling. Currently, generic medicine package inserts can only be updated after their innovator medicines have been updated. The information on the generic medicines product information has to be the same as the innovator product information (FDA-2013-N-0500).

On November 13, 2013, the FDA issued a proposed rule regarding Supplemental Application proposing labeling changes for Approved Drugs and Biological products. This legislative proposal by FDA will impose liability on generic manufacturers for discovering and reporting new adverse effects. The proposal would ensure that latest safety information is available for generic medicines, but their labels would differ from innovator medicines and also amongst the generic medicines on the market. The proposed rule creates an environment whereby different labeling, including different warnings, can simultaneously exist in the marketplace for the same medicines (GPhA, 2014). The proposed rule will create differences in medicine labeling which will cause confusion in the market, but this rule will also ensure that generic medicines PIs are updated in time to warn healthcare professionals and patients about the possible risk of medicines.

In South Africa there is no binding rule to update package inserts between innovator and generic medicines. Generic medicines applicants are not expected to wait for innovator product PIs to be updated before they could submit package inserts for safety updates, but a PI for the innovator has to be submitted as part of the references for the application of generic medicine amendment. Applicants for generic medicines can also use information from other regulatory authorities with which the council is aligned, such as the FDA and EMA, to update their package inserts (PI guideline, 2014).

2.3. Package inserts in other countries

This study compared the package inserts from different manufacturers (innovator and generic companies) as approved in South Africa. No studies were found that had been done in South Africa on package insert information content. Examining the situation in other countries gives some information of what is happening globally.

The study conducted in Southern India indicates that information relevant to safe and effective use of medicines was not mentioned in the analyzed package inserts. However, this study checked for the presence of information in each heading (Deepak, Ananya, Swaroop, Syed, Praveen, & Srinivas, 2013). This study also found that the clinical information in package inserts need to be further refined to minimize the risks to patients, and that information available to healthcare professionals is often outdated (Shivkar, 2009).

The package inserts for the same medicines were found to vary in detail in Japan, USA and UK. It was found that information on pharmacokinetic interactions of calcium antagonists in the PIs from these three countries differ. The PIs in the USA provided a great deal of quantitative information in contrast to those in the UK. The ones in Japan did not provide sufficient information. The study also indicated that differences in the description of the PIs for each calcium antagonist between countries may reflect the differences in the attitude of the regulatory authorities (Mitsuo, Mutsuku, Shinji, Ryuichi, 2005).

A package insert is an important document containing information that communicates the risks of medicines. In certain instances, there can be reasons why package inserts of the same medicines or same molecule contain different safety information, but to eliminate confusion amongst healthcare professionals, information should be harmonized. Such differences may result in patients being confused while using generics and innovator products, as the information in the PILs would contain different information. The PILs that are made available to the patients are compiled in line with the PI and the possibility is high that if the PI has deficient information, then the PIL will also be deficient. The process of package insert safety updates will have to be refined to ensure consistency amongst the package inserts of innovators and generics available to the public, and to minimise risks and promote safety.

CHAPTER 3: METHODOLOGY

Data was collected from two classes of medicines viz. statins and anti-hypertensives. A list of registered statins and anti-hypertensive medicines was sourced from the MCC registered products database in South Africa. The PIs were traced from the Clinical unit database and sourced from the filing room. The different company names and the trade names of medicines were alphabetically coded. This was a retrospective qualitative study.

The statins identified from the database were simvastatin, fluvastatin, atorvastatin and rosuvastatin from different companies. The anti-hypertensives chosen were enalapril maleate, amlodipine, nifedipine and irbesartan.

The PIs of combination medicines were excluded from the study and innovator medicines with generics that could not be traced or located were excluded from the study e.g. fluvastatin. Some of the products that could not be traced on the clinical database were also excluded from the study.

To determine if the package inserts of generics contained the same safety information as innovator products both statins and anti-hypertensive medicines PIs were assessed. The latest approved innovator medicine package inserts were compared with their generic medicines PIs. Twenty-five package inserts located from the clinical database and sourced from the clinical unit filing were assessed and analysed. The data was tabulated reflecting each section of the package insert assessed. These sections were: pharmacological action (pharmacodynamics and pharmacokinetics), indications, contra-indications, warnings and special precautions, interactions, dosage and directions for use, pregnancy and lactation, side-effects and known symptoms of overdosage and particulars of its treatment.

The information in each section of the package insert in generics was compared with the ones in the innovators; the wording needs not be the same. Information about which sections vary or are similar between generic medicines and innovator PIs was determined.

To assess the process of medicine package insert amendments, innovator and generic medicines (statins and anti-hypertensives) applications submitted for package inserts amendment were assessed. References submitted with amendments of package inserts, submission and approval dates were noted; this also included few generic applications for registration to assess what references are submitted for generic medicines approvals. This was done to determine any factors that may contribute to any deviations that may be observed between the innovator and generic medicines PIs.

CHAPTER 4: FINDINGS AND ANALYSIS/DISCUSSION

4.1 Comparing innovator and generic medicine package inserts to check whether the safety information of these PIs were the same.

TABLE 1: Package inserts information on simvastatin innovator and generic products

PD-pharmacodynamic properties PK - pharmacokinetic properties Lu- last update of the package insert

PACKAGE INSERT HEADINGS	INNOVATOR(A) Lu:2000	GENERIC(E) Lu:2013	GENERIC(B) Lu:2011	GENERIC(C) Lu:2007	GENERIC(D) Lu:2005
PHARMACOLOGICAL ACTION	Same PD No PK information	Same PD PK information available	Same PD PK information available	Same PD PK information available	Same PD PK information available
INDICATIONS	Same	Same	Same	Same	Same
CONTRA-INDICATIONS	Same	Same	Same	Same	Same
WARNINGS AND SPECIAL PRECAUTIONS	Same	Same	Same	Same	Same
INTERACTIONS	Less updated	More updated	More updated	More updated	More updated
PREGNANCY AND LACTATION	Nothing	More updated	Updated	Updated	Updated
DOSAGE AND DIRECTION FOR USE	Same	Same	Same	Same	Same
SIDE-EFFECTS	Less updated	More updated	More updated	More updated	More updated
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT	Same	Same	Same	Same	Same

Table 1 above compared information content of simvastatin innovator and generics. The innovator PI was last updated in 2000. The pharmacokinetic information differed. The innovator did not have any pharmacokinetic information. The innovator did not have a heading and information on pregnancy and lactation. The interactions and side-effects sections showed that the generics PIs included additional updated information.

The other sections viz. Indications, contra-indications, warnings and special precautions, dosage and direction for use and known symptoms of overdose and particulars of its treatment contained the same information as those of the innovator.

Table 2: Package inserts information on rosuvastatin innovator and generic products

PD-pharmacodynamic properties PK- pharmacokinetic properties Lu- last update of PI

PACKAGE INSERT HEADINGS	INNOVATOR(F) Lu:2012	GENERIC(G) Lu:2013	GENERIC (H) Lu:2013
PHARMACOLOGICAL ACTION	Same	Same	Same
INDICATIONS	Same	Missing some indication	Same
CONTRA-INDICATIONS	Less updated	More updated (with addition of severe renal impairment and patients with predisposing factors for myopathy/rhabdomyolysis.	More updated same as generic (G)
WARNINGS AND SPECIAL PRECAUTIONS	No warnings	More updated	More updated
INTERACTIONS	Less updated	More updated	More updated
PREGNANCY AND LACTATION	Safety in pregnancy and lactation has not been established	Pregnancy and lactation contra-indicated. TN (trade name) may cause serious congenital defects.	Pregnancy and lactation contra-indicated.
DOSAGE AND DIRECTION FOR USE	Covers children and adolescents 10-17 years of age with familial hypercholesterolemia	Not the same(missing some dosage)	Not the same (missing some dosage)
SIDE-EFFECTS	Less updated	More updated	More updated
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT	Same	Had an additional sentence “ liver function and CK levels should be monitored”	Same

Table 2 above compared information of rosuvastatin innovator and generics. The only section where information was the same was for pharmacological action for both generics. Indications were the same as in generic (H) and also known symptoms of overdose and particulars of its treatment. All the other sections contained varying information.

Table 3: Package inserts information on atorvastatin and generic products

PD-pharmacodynamic properties PK - pharmacokinetic properties Lu- last update of PI

PACKAGE INSERT HEADINGS	INNOVATOR(I) Lu: 2009	GENERIC(L) Lu: 2012	GENERIC(J) Lu: 2014	GENERIC(K) Lu: 2013
PHARMACOLOGICAL ACTION	Same	Same	Same	Same
INDICATIONS	Same	Less indications	Less indications	Same
CONTRA-INDICATIONS	Same	Same	Same	Same
WARNINGS AND SPECIAL PRECAUTIONS	Same	Same	Same	More updated
INTERACTIONS	Same	Same	Same	More updated
PREGNANCY AND LACTATION	Same	Same	Same	Same
DOSAGE AND DIRECTION FOR USE	Same	No dosage for cardiovascular complication	No dosage for cardiovascular complication	Same
SIDE-EFFECTS	Same	Same	Same	Same
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT	Same	Same	Same	Same

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Table 3 above compared information content of atorvastatin and generic products. In this case the information differed under indications and dosage and directions for use. The innovator had more indications than the generics and additional information was included on dosage and directions for use. The other sections contained the same information. Generic (K) dated 2016 had updated information under warnings and special precautions and interactions.

Table 4: Package inserts information on amlodipine innovator and generic products

PD- pharmacodynamic properties PK - pharmacokinetic properties Lu - last update of PI

PACKAGE INSERT HEADINGS	INNOVATOR (M) Lu: 2008	GENERIC (N) Lu: 2011	GENERIC (O) Lu: 2012
PHARMACOLOGICAL ACTION	Same	Same	Same
INDICATIONS	More indications including: chronic stable angina	Angina pectoris Mild and moderate hypertension	Angina pectoris, mild to moderate hypertension
CONTRA-INDICATIONS	Same (only hypersensitivity to ingredients)	Same (only hypersensitivity to ingredients)	More contraindication; Severe hypotension, shock, heart failure, unstable angina, obstruction of the outflow-tract of the left ventricle.
WARNINGS AND SPECIAL PRECAUTIONS	Same	Same	Same
INTERACTIONS	Less updated	More updated	More updated
PREGNANCY AND LACTATION	Same	Same	Same
DOSAGE AND DIRECTION FOR USE	Additional dose for coronary artery disease	No additional dose for coronary artery disease	No additional dose for coronary artery disease
SIDE-EFFECTS	Same	Same	Same
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT	Same	Same	Same

Table 4 above compared information content of amlodipine innovator and generics. The information was the same for pharmacological action, warnings and special precautions, pregnancy and lactation, side-effects and known symptoms of overdose and particulars of its treatment. The innovator had additional indications and additional dosages for the indications while one generic product had more contra-indications.

Table 5: Package inserts information on enalapril innovator and generic products

Lu- last update of PI PD-pharmacodynamic properties PK-pharmacokinetic properties

PACKAGE INSERT HEADINGS	INNOVATOR(P) Lu: 2013	GENERIC (R) Lu: 2012	GENERIC(Q) Lu: 2014
PHARMACOLOGICAL ACTION	Same	Same	Same
INDICATIONS	Same	Same	Same
CONTRA-INDICATIONS	Same	Same	Same
WARNINGS AND SPECIAL PRECAUTIONS	Same	Same	More updated
INTERACTIONS	Same	Same	More updated
PREGNANCY AND LACTATION	Same	Same	contra-indicated in breastfeeding while innovator state use with caution
DOSAGE AND DIRECTIONS FOR USE	Same	In creatinine clearance less than 30ml/min the dosage is reduced while innovator state contra-indicated.	Same
SIDE-EFFECTS	Less side-effects	More updated	More updated
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT	Same	Same	More symptoms of overdose.

Table 5 above compared information content of enalapril innovator and generics. The innovator was last updated in 2013. The information was the same under pharmacological action, indications and contra-indications. Generic (R) dated 2012 had a reduced dosage for patients with severe renal impairment even though in this patients the medicine is contra-indicated according to the PI while the innovator clearly state contra-indicated with no dosage at all. In the PI for Generic (Q) under pregnancy and lactation, the medicine is contra-indicated in breastfeeding while the innovator state that it should be used with caution. More symptoms of overdose are also stated in Generic (Q) than the innovator. Warnings and special precautions and side-effects are also more updated in Generic (Q) than the innovator.

Table 6: Package inserts information on nifedipine innovator and generic products

PD-pharmacodynamic properties PK- pharmacokinetic properties Lu- last update of PI

PACKAGE INSERT HEADINGS	INNOVATOR(S) Lu: 2008	GENERIC(T) Lu: 2013	GENERIC(U) Lu: 2011	GENERIC(W) Lu: 2015
PHARMACOLOGICAL ACTION	Same PD differs in pharmacokinetics	Same	Same	Same
INDICATIONS	Same	Same	Same	Same
CONTRA-INDICATIONS	Same	Same	Pregnancy and lactation not contra-indicated	Same
WARNINGS AND SPECIAL PRECAUTIONS	Same	Same	Less updated Added some of the conditions that are already contra-indicated as warnings with text like use with caution	Different from the rest
INTERACTIONS	Same	Same	Same	Same
PREGNANCY AND LACTATION	Contra-indicated before week 20	Same	Pregnancy and lactation not contra-indicated but state that it should not be used.	Safety in pregnancy and lactation has not been established
DOSAGE AND DIRECTION FOR USE	Same	Same	Same	Same
SIDE-EFFECTS	Same	Same	Less updated	More updated
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT	Same	Same	Same	Same

Table 6 above compared information content of nifedipine innovator and generics, the innovator was last updated in 2008. Information was the same for pharmacodynamic properties, indications, interactions, dosage and direction for use and known symptoms of overdose and particulars of its treatment. For contra-indications, warnings and special precautions, pregnancy and lactation and side-effects the information was not consistent.

Table 7: Package inserts information on innovator irbesartan and generic products

PD - pharmacodynamic properties PK - pharmacokinetic properties Lu - last update of PI

PACKAGE INSERT HEADINGS	INNOVATOR (X) Lu:2012	GENERIC(Y) Lu:2013	GENERIC(Z) Lu: 2012
PHARMACOLOGICAL ACTION	Same	Same	Same
INDICATIONS	Same	Same	Same
CONTRA-INDICATIONS	Same	Same	Same
WARNINGS AND SPECIAL PRECAUTIONS	Same	Same	Same
INTERACTIONS	Same	More updated	Same
PREGNANCY AND LACTATION	Same	Same	Same
DOSAGE AND DIRECTION FOR USE	Same	Same	Same
SIDE-EFFECTS	Same	Same	Same
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT	Same	Missing statement "However daily doses of up to 900mg/day for 8 weeks were well tolerated"	Same

Table 7 above compared information content of irbesartan innovator and generics. The package insert of innovator was last updated in 2012 and the information was the same as a generic that was also updated in 2012 for all sections. A generic that was updated in 2013 included additional information with respect to interactions compared to the innovator.

In total twenty-five PIs were evaluated by comparing those of generic medicines to innovator ones. The first difference noted was in terms of their headings. Recently updated PIs included the sections on pregnancy and lactation, warnings and pharmacokinetic while these were not included for some of the previously updated PIs. The sections evaluated and compared with the innovator PIs were pharmacological action, indications, contra-indications, warnings, interactions, pregnancy and lactation, dosage and directions for use, side-effects and known symptoms of overdose and particulars of its treatment.

The evaluated PIs showed that 34% of Information in innovator medicines PI was different to the generic medicines and that 66 % was the same.

Table 8: Package inserts information content between innovator and generic medicines.

Sections of the package inserts	Same information	Different information
Pharmacological action	73.5%	26.5%
Indications	76%	24%
Contra-indications	72%	28%
Warnings and Special precautions	72%	28%
Interactions	44%	56%
Pregnancy and lactation	56%	44%
Dosage and direction for use	64%	36%
Side-effects	48%	52%
Known Symptoms of overdose and particulars of its treatment	88%	12%

Differences were observed for the sections viz. interactions, side-effects, pregnancy and lactation, dosage and directions for use, contra-indications and warnings and special precautions. These differences were not as pronounced for the sections on pharmacological action, indications and known symptoms of overdose and particulars of its treatment.

Package inserts approved in the same year or in consecutive years did not reflect major differences in information content. That was noticed in table 7 above.

Important sections of the package insert such as contra-indications contained information which differed from what is in the innovator and generics PIs. This can lead to confusion and may cause detrimental effects to the patients who use different brands of the same medicine. Pregnancy and lactation also contained inconsistent information.

Recently updated generics PIs were found to have included additional information on side-effects, warnings and special precautions and interactions, while the innovator medicine PIs included more indications and dosage and direction for use. The reason some generic medicines PIs include fewer indications may be due to the restrictions related to patent protection. The generic manufacturer can only market generic medicines once the period of exclusivity on the innovator products has expired. Innovator companies can use patent law to further restrict the generic companies from adding new indications for previously registered medicines.

Known symptoms of overdosage and particulars of its treatment contained the most consistent information in the PIs. The only differences were with some PIs stating more symptoms of overdose.

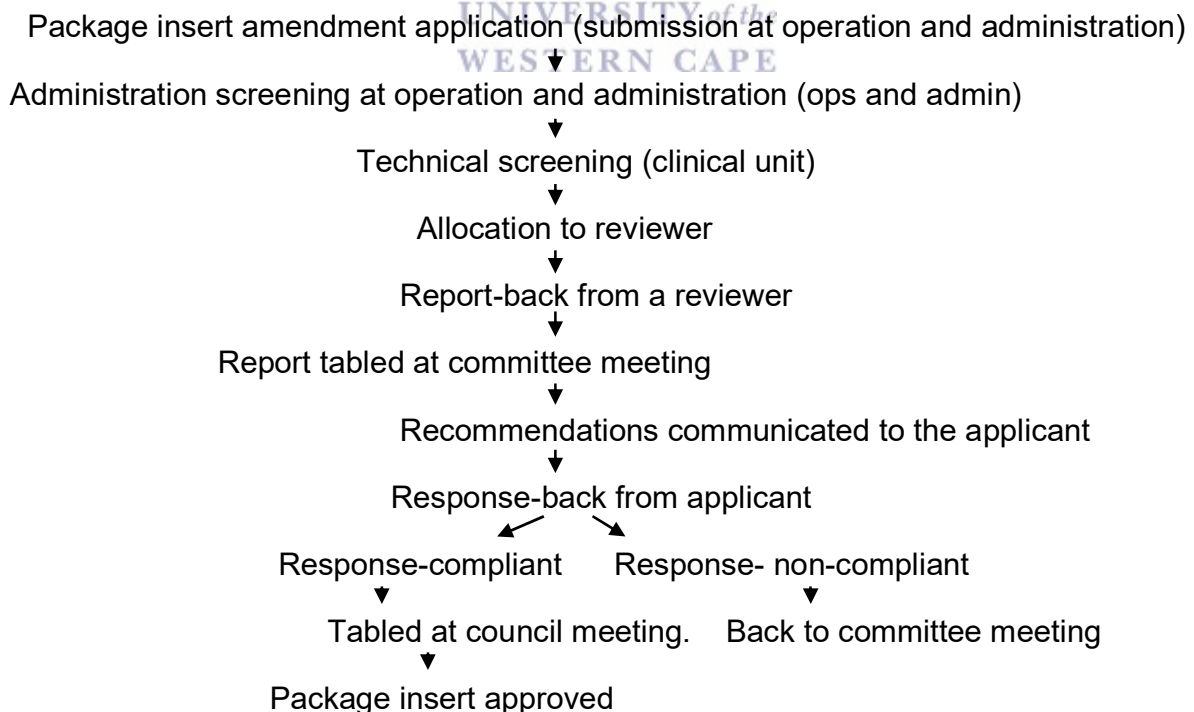
Some of the package inserts of the innovator medicines listed in the tables above were outdated and that may have contributed to the differences found when they were compared to the generic medicines PIs. It clearly shows that the generic medicines PIs of these innovator medicines may have been updated with the latest safety information from other acceptable references other than the innovator PIs.

4.2 The process of generic medicine PI amendments

The process of PI amendment involves different steps in South Africa. The flow diagram below shows the stages that an application for an amendment has to follow.

This involves administration screening until the package insert is approved by the council. If the application is not compliant with some of the committee recommendations, the application is tabled at the relevant committee again. This process can be ongoing until agreement is reached between the committee and the applicant.

Figure 1: flow diagram of package insert amendment process.



A number of steps are involved for PI-amendment and as such it is understandable that delays may occur at any of these. This can be on the side of the regulator if the response is not communicated to the applicant in time or by the applicant if the submission is not as required. This may relate to major deficiencies with the submission and the applicant not complying with the standards as stipulated in the MCC guidelines.

The sample of products that were compared with their innovators in Table 1 to Table 7 were also used to assess the amendment process in Table 9, this might give an inside view of the differences in some of the generic package inserts that just got registered or recently amended PIs and their innovator PI.

The process of package insert updates and registration requires the submissions to be accompanied by acceptable references. Below is a table indicating the submission dates, the references that the applicants used during amendments and during registration of generics, and the approval dates. The references submitted indicate that, for the approval of generics, other references are accepted during registration in addition to the innovator PIs.

The references submitted in support of the registration included locally registered innovator PIs, supportive data from regulatory bodies with which MCC aligns itself such as the Food and Drug Administration (FDA) and United Kingdom regulatory agency, and other acceptable references like Goodman and Gilman, and Martindale.

Table 9: Registered generic medicines applications submitted for safety update /amendment and some applications submitted for registration were included. The products and companies were alphabetically coded.

TABLE 9: GENERIC MEDICINES UPDATES

PRODUCT	ACTIVE INGREDIENT	DATE OF UPDATE /REGISTRATION SUBMISSION DATE	REFERENCES USED BY THE APPLICANT FOR UPDATE/REGISTRATION	APPLICANT	DATE FINALIZED/APPROVED
(A)	simvastatin	April 2006	-Safety update -Information on references could not be traced	(AA)	Not finalised
(B)	simvastatin	February 2009	-Safety update -Zocor. Prescribing information. Merk & Co. Inc.USA. June 2008 - USPDI, Micromedex Thomson Healthcare, 22nd edition, 2002 - Martindale -The Complete Drug Reference, Accessed from The Micromedex Healthcare Series.	(BB)	November 2011
(C)	simvastatin	June 2012	-Safety update FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs, safety announcement 28 February 2012. -FDA safety communication: interaction between certain HIV or Hepatitis-C drugs and cholesterol-lowering statins can increase the risk of muscle injury, safety announcement 2012. -FDA approved reference product Zocor tablets, revised 02/2012	(CC)	Not finalised
(D)	simvastatin	July 2012	-Safety update -UK SPC of Zocor dated 22 May 2012 -US-approved prescribing information, revised June 2012 -Locally approved PI for Zocor dated 2000	(DD)	Not finalised
(E)	simvastatin	September 2006	-Application for registration -SPI for simvastatin	(EE)	Registered June 2014
(F)	rosuvastatin	July 2010	-Safety update -Company core data sheet (CCDS)	(FF)	October 2012

(G)	rosuvastatin	July 2013	Amendment involved removal of indication to avoid patent infringement.	(GG)	June 2015
(H)	rosuvastatin	November 2010	-Application for registration -Innovator PI, Crestor 2008 -SPC Crestor Astra Zeneca UK -Goodman and Gilman, 11 th edition -Martindale online version 2010 -USPDI, VOL.26, 2006	(HH)	Registered August 2013
(I)	atorvastatin	August 2013	-Safety update -Medicines Control Council, Pharmacovigilance communication dated May 2012 -FDA Drug Safety Communication -FDA prescribing information - European Medicines Agency, 10 January 2012, EMA/CHMP/PhVW/973945, Patient Health Protection. -Case report of rhabdomyolysis with concurrent colchicines and atorvastatin.	(II)	February 2016
(J)	atorvastatin	December 2016	-Safety update -Artovastatin core data sheet, version 16.0, dated 12 April 2016 -UK SMPC Lipitor 80 mg dated March 2016 -USPDI Lipitor tablets dated March 2015	(JJ)	Not finalised
(K)	atorvastatin	August 2013	-Safety update -Medicines Control Council, Pharmacovigilance Committee recommendation dated 23 May 2012	(II)	April 2016
(L)	atorvastatin	March 2011	-Application for registration -Innovator PI: Lipitor tablets range -Martindale 35 th Edition	(LL)	Registered 2013
(M)	amlodipine	November 2014	-Safety update -Amlodipine besilate core data sheet version 9.0 10 July 2014 including references on which the core data sheet is based e.g. study reports and articles.	(II)	Not finalised
(N)	amlodipine	December 2014	-Safety update -SPC dated 09 October 2014 for focus pharmaceutical LTD Amlodipine 10mg tablets. -Pfizer's Norvasc US PI revised May 2011 -Martindale 38 th Edition -USP DI 27 TH Edition	(NN)	September 2017

(O)	amlodipine	November 2010	-Safety update -Global core data sheet: Amlodipine oral dated May 2008 -Statement on changes to the core data sheet on Amlodipine, May 2008 -USP DI, 27 Edition -European journal of Clinical pharmacology. - Drug induced taste and smell disorders, Drug safety, 1994. -Quantification of leg oedema in postmenopausal hypertensive patients treated with lercanidine or amlodipine(2003)	(OO)	2012
(P)	enalapril maleate	December 2009	-Safety update -Information on references could not be traced	(PP)	2013
(Q)	enalapril maleate	2012	Company Core Data Sheet(CCDS)	(QQ)	2014
(R)	Enalapril maleate	April 2006	-Application for registration -Innovator PI: Renitec range dated 2006. -Goodman and Gilman's, the pharmacological basis of therapeutics, 11 th edition 2001	(RR)	Registered 2012
(S)	nifedipine	APRIL 2010	-Safety update -Company Core Data Sheet (CCDS)	(SS)	July 2016
(T)	nifedipine	August 2013	-Safety update - Company Core Data Sheet version 15-16 dated 01 December 2009	(SS)	July 2016
(U)	nifedipine	FEBRUARY 2015	- Safety update Adalat XL innovator PI -UK SPC for ADALAT Retard, dated Feb 2014. -Martindale 38 th edition, monograph for nifedipine	(NN)	Not finalised
(W)	nifedipine	December 2007	-Application for registration -approved PI for Vascard 30 SR dated 1999 - USP DI 2006	(WW)	Registered 2015
(X)	irbesartan	May 2012	-Safety update - Company Core Data Sheet/global labeling	(XX)	Not finalised
(Y)	irbesartan	December 2008	-Application for registration -Innovator PI Approval extracted from MIMS Desk Reference 2008 -Goodman and Gilman, <i>The pharmacological basis of therapeutics</i>	(WW)	Registered 2013

			-Martindale, <i>The Complete Drug Reference</i> .		
(Z)	irbesartan	May 2012	-Safety update -Company Core Data Sheet -Irbesartan. Clinical overview for Renal Impairment/Failure	(HH)	Not finalised

The package inserts of the products that had no submissions for amendments were also included, but instead of including the references for amendments, the references used for registration purposes were included in the table. These were six-package inserts, and by assessing these submissions, it showed that it took a period of 2 years to 8 years for generic medicines to be approved. The innovator's package inserts were included as part of the references in some of these applications, but by the time registration took place the innovator's package inserts were already outdated. Other references were also included during registration as can be seen in table 9 above. This may have contributed to the differences or inconsistencies in the information content of the innovators and generic medicines PIs that just got registered. The package insert approvals during registration showed that a generic medicine that has just been registered may contain information varying from that of the innovator PI since the innovator PI is not the only reference accepted during registration. This implies that a generic medicine PI can contain information differing from that of the innovator PI just after its registration, even before any amendment.

The data above also showed that for package insert amendment to be approved, it can take a period of four years after application submission. Approval of applications usually occur within 2 years, but in one of the cases above it took 11 years. Delays in approval of amendments may contribute to variation in the package inserts, both when the applications are going through the process of approval and when responses to these applications are not evaluated at the same time. The MCC does not have timelines for post-registration approval of PI updates. For urgent safety alerts, Dear Health Care Professional letters (DHCPL) are sent out within 30 days by the pharmacovigilance unit while the PIs are still in the process of being updated.

Amendments to package inserts may be made for different reasons. Most of the innovator PIs were amended to be brought in line with company core data sheets, but the references on which the core data sheets are based should also be submitted according to the PI guideline. Some of the changes were prompted by the Pharmacovigilance

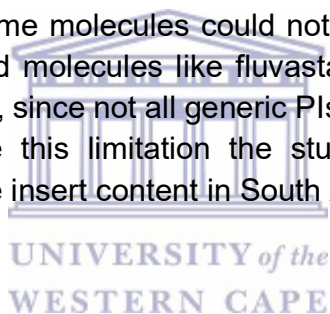
recommendation after a safety alert and also safety alerts from other regulatory authorities with which the council aligns itself, as can be seen from the table above.

Including other references in addition to the innovator medicine PI during submission for an amendment is useful in order to ensure that generics PIs in the market contain the latest safety information, especially when the innovator PI was last revised a long time ago. One of the applications for amendment was to remove the indication to avoid patent infringement, and this means the indications will now be inconsistent with those of the innovator. With various references that can be used in support of a package insert amendment, a variation is likely to exist in information contained in the package inserts.

As seen above, submission at different times of applications for medication using the same active ingredients may result in variation not only with innovator PIs but also amongst generic medicine PIs.

Limitations of the study

Some of the generic PIs for some molecules could not be traced and located from the Clinical database. This included molecules like fluvastatin. Not all molecules could be compared with their generic PIs, since not all generic PIs could be traced or located from the Clinical database. Despite this limitation the study represents one of the first researches to evaluate package insert content in South Africa.



CHAPTER 5: CONCLUSION AND/OR RECOMMENDATIONS

5.1 Conclusion

The information in the package inserts of the innovator medicines differ from that of generic medicines as shown by the analysis and the discussion above. The regulator does not have specific conditions or does not prioritise innovator medicines PIs when it comes to amendments. Generic medicines can be amended irrespective of whether a latest innovator package insert is available or not. It is seen on the available data that some generic medicines were amended even though some of the innovator medicines were last updated a long time ago. The package inserts guideline for South Africa (2013) states that at least the indication(s), the dosage and safety profile of the generic medicine must be the same as on the innovator package insert.

It is acknowledged that even though the package inserts of the innovators and generics were different in some sections of the PI, the latest safety information was included with amendments of generic medicines applications from other acceptable references. The amendments did not entirely rely on innovator medicine PIs.

The fact that the regulatory authority accepted other references and not only the innovator PI for amendments of package inserts contributed to differences in the PIs content of generics and innovator medicines. If these other references were not accepted then generic medicines PIs would contain outdated information, since some of the PIs of innovator medicines were outdated as seen above. The package inserts with the latest safety information should be available for healthcare professionals and the public to minimise the risks of medicines. The package inserts of similar medicines should be harmonised to contain the same information in the PIs and therefore ensure consistency in information content.

5.2 Recommendations

The WHO (1998) states that well-resourced agencies find it impossible to evaluate all pharmaceutical changes made to all products, and it is therefore necessary to define those changes that can be made without the involvement of regulatory authorities. In South Africa the safety-related package insert notifications (SRPINs) can be submitted by applicants for minor changes, for example adding side-effects (SR-PINs, 2014). The applicant can implement the changes after 60 days of sending a notification. Furthermore, according to the WHO, if resources are limited, as is the case in South Africa, a better approach is to update products in groups, beginning with perhaps essential medicines, medicines with life-threatening diseases, and medicines or groups of medicines for which there are important new discoveries in safety and efficacy. Grouping of medicines or

classes of medicines and the clinical committee evaluating these medicines simultaneously would eliminate variations between the PIs of innovator and generic medicines.

A well-integrated system or computer system is required to trace applications easily at each step of the process. A system that would ensure that all incoming applications are allocated in a strategic way that would place the products with the same molecules together, taking into consideration the time they were submitted. This would ensure that the package inserts of the same molecules are evaluated simultaneously and contain similar information and are consistent. This would eliminate variations and missing information in some package inserts.

There could be more consistency with the information on the PIs if the innovator manufacturer submitted their package inserts safety update just before the generic medicines PIs or if both submitted at the same time or even for the regulator to prioritise innovator package inserts or evaluate both at the same time since most of the generic PIs depend on the updated information of the innovator PIs.

Further research needs to be done on the factors that may delay package inserts approvals for amendments; this may improve the current system (processes) of the regulatory authority. To ensure that applications be processed as soon as possible, the regulatory authority needs adequate staff and resources to carry out these functions efficiently.

If latest innovator package inserts were made available on the MCC website to ensure that applications for generics have been aligned with the innovator PIs before submission, or the latest approved PI of either a generic or innovator of a certain molecule be made available at the website and the rest of the products with the same molecules be brought in line with the website PI, these would eliminate variation in information in different PIs.

Availability of standardised text for different classes of medicines on the website e.g. Warnings and Special Precautions for antiretroviral medicines is important for consistency in the content of the package inserts; these is available on the MCC website but more classes of medicines should also be included to promote consistency for example statins.

The innovator manufacturers should be made aware if their package inserts are outdated and be requested to update. When changes are made to the generic PIs, the innovator PIs manufacturers should be requested to make the same changes at almost the same time. The generic PIs manufacturer should ensure that the latest innovator PI is included with the submission of an amendment at all times.

Harmonisation of package inserts containing the same molecule (innovator and generic PIs) will eliminate confusion to the public and healthcare professionals when referring to the package inserts.



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Appendix 1:

RESEARCH PROPOSAL

FOR

MABUNDA HITEKANI TOLERANCE

STUDENT NO: 3378671

OCTOBER 2012 COHORT



TABLE OF CONTENTS

1. Research proposal.....	page 42-43
2. Ethical considerations.....	page 44
3. References.....	page 44



RESEARCH PROJECT PROPOSAL

Title: Innovator medicines versus generic medicine package inserts safety amendments, the reality in South Africa.

Introduction

This research was triggered by comments passed by the expert committee (Clinical Committee) that met to discuss the package insert amendment of the generic medicines. They advised that the information on the pharmacodynamic properties of the generic medicine package insert be brought in line with that of the innovator medicine package insert. Examination of these medicine package inserts showed that the pharmacodynamic properties were totally different. This prompted the investigation to ascertain if this was a rare event or if this was the case with generic medicines PIs. Certain sections of the PIs do differ between innovator and generics particularly the composition in which the excipients may differ. This also applies to the presentation section where the colour and shape differs.

To register a generic medicine in South Africa there must be a South African registered medicine for use as a reference and bioequivalent studies must be submitted to show that they have the same stability and bioavailability.

In the USA the generic medicine manufacturer for which updated product safety is available can only proceed once the updated safety information of the corresponding brand name product has received approval for update. In November 2013 the FDA took action to speed safety information update on generic medicines by proposing that generic drug manufacturers will be able to independently update product labeling with newly acquired information before the FDA's review of the change. This is the same process innovator drug manufactures do today. Generic manufacturers would be required to inform the innovator manufacturers about the change.

In South Africa there is no specific binding rule when it comes to amendment of generics, any change that is made to the package insert by either the innovator or the generic medicine manufacturer must be substantiated by evidence of acceptable references. This might cause discrepancies as the content of the package inserts might differ between innovator and generic medicines. The innovator medicine manufacturer may not update their package inserts for a long time but generic medicine manufacturers can still update their package inserts and not rely on innovator PIs.

The Medicines Control Council has at the website “package insert standardised texts” for various classes of medicines. These texts are to be included in package inserts of generic or innovator medicines that falls within a specific class as stipulated by the guideline. The applicant has to include this text during compilation of the package insert.

These texts can be warnings and special precautions, safety information or other. The purpose of this guideline is to ensure that safety information that affects the class of medicines is included in each medicine PI that falls within that class and that there is consistency in the package inserts content. This research aims to find out whether the content of the package inserts are the same between innovator and generic medicines. It is important that the safety information in the package inserts of medicines with same molecule (active ingredient) contain the same information even though the wording need not be identical, as these products can be used interchangeably. This is of value to the prescriber and patient.

The aim

1. To investigate if the package inserts of generic medicines contain the same safety information as the package inserts of innovator medicines.
2. To assess the process of package inserts amendments

Methodology

1. A list of registered generic medicine package inserts will be checked against their innovator medicines. This information will be accessed from the Clinical unit database where the innovator medicines will be identified and also their generics. The package inserts will be pulled out and the content of the package inserts will be compared against each other. Generic medicine package inserts will be checked against their innovator medicines package inserts.
2. To assess the process of generic and innovator medicine package inserts amendment, a list of the registered selected medicines will be sourced from a database of MCC and the package inserts approval date, submission dates of these selected medicines and references will be accessed from the clinical database.

Ethical considerations

1. Permission sought from Director General of Health to collect and use data from the database of Medicines Regulatory Affairs.
2. Companies names, details and product names were alphabetically coded.

References

1. FDA news release: FDA takes action to speed safety information updates on generic drugs, 8 November 2013.
2. Gaffney, A. (2014), Regulatory explainer: understanding the regulation of generic drug labels
3. Kreisberg, J. (2013), Recommended reading:” A first amendment application to generic drug manufacture Tort liability
4. MCC (Medicines Control Council), *Package insert for human medicines standardised texts*, at <http://www.mccza.com>, accessed: May 2014

