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A COMPARISON OF THE PACKAGE INSERTS OF ORIGINATOR BRANDS AND GENERIC MEDICINES REGISTERED BY AN INTERNATIONAL PHARMACEUTICAL COMPANY

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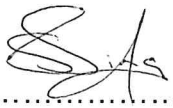
Co-supervisor: Dr Kerryn Dixon

A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, in partial fulfilment of the requirements for the Degree of Master of Science in Medicine (Pharmaceutical Affairs)

Johannesburg, November 2018

DECLARATION

I, Shaistha Sing, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine (Pharmaceutical Affairs) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



.....

7th day of November, 2018

DEDICATION

To my parents, Kamal and Razia Sing, who have always taught me to never give up on my dreams.

Everything I am, and everything that I aspire to be is because of you.

I thank you for all the sacrifices that you have had to make so that I could grow and achieve

all that was in my path.

My biggest fans and my greatest champions, I love you

ABSTRACT

Over the past few years the usage of generic medicines has been increasing, mainly as a means to lower costs in the delivery of healthcare. But, the availability of generic medicines does come with its own set of potential problems which create doubt and a lack of confidence with the use of generic medicines. The package insert provided as a source of written information, accompanies a generic medicine. The originator medicine package insert is used as the primary source of information when compiling a generic medicine package insert hence it is easy to assume that the information provided in both package inserts would be the same. The South African Health Products Authority (SAHPRA) has the task of reviewing and approving the information that is presented in a generic medicine package insert. Previous research carried out has identified that there are significant differences in the information provided in package inserts of originator and generic medicines. This study was carried out to describe the differences noted in the package insert of generic medicines registered by an international pharmaceutical company in comparison to the information provided in the corresponding originator medicine package insert (PI) registered in South Africa. A textual analysis was used to compare the information presented in the PIs. The regulatory staff at generic pharmaceutical companies are responsible for compiling the package insert. A focus group discussion was conducted with the regulatory staff of a generic pharmaceutical company that is based in Johannesburg. The pharmaceutical company is one of the world's leading generics and specialty pharmaceutical companies. Key findings from this study demonstrate that there are considerable differences between the information presented in the originator and generic medicine PIs. The differences noted can be attributed to the sources of information used by regulatory staff for the compilation of a generic medicine package insert as well as the health authority review process that is carried out prior to the approval of the package insert. The current system used by the health authority for the evaluation of generic medicine package inserts is flawed. Communication with the health authority is challenging and the lack of transparent processes contribute to a delay in the approval of generic medicine package inserts. The findings from this study indicate an urgent

need to address the current South African registration system with respect to the labelling of generic medicines.

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NOMENCLATURE

ACE inhibitors: Angiotensin Converting Enzyme Inhibitors

API: Active Pharmaceutical Ingredient

ARB's: Angiotensin Receptor Blockers

AUC: Area under the curve

BSA: Body Surface Area

CCR: Clinical Committee Recommendation

CHMP: Committee for Human Medicinal Products

COX2: Cyclooxygenase-2

CyP34A: Cytochrome P34A

ECG: Electrocardiogram

EMA: European Medicines Agency

eMC: Electronic Medicines Compendium

EU: European Union

GGT: Gamma-glutamyltransferase

GPs: General Practitioners

GPI: Generic Package Insert

HCTZ: Hydrochlorothiazide

HIV: Human Immuno Deficiency Virus

HOCM: Hypertrophic Cardiomyopathy

INR: International normalised ratio

IPI: Inactive Pharmaceutical Ingredient

MCC: Medicines Control Council

MCHC: Mean Corpuscular Hemoglobin Concentration

MRA: Medicine Regulatory Authority

NSAIDS: Non-steroidal anti-inflammatory drugs

OPI: Originator Package Insert

PI: Package Insert

PIL: Patient Information Leaflet

QT: Cardio Contraction

QTC: Cardio Contraction Time

SAHPRA: South Africa Health Products Regulatory Authority

SmPC: Summary of Product Characteristics

TGA: Therapeutic Goods Administration

UK: United Kingdom

US: United States

USP: United States Pharmacopeia

UTI: Urinary Tract Infection

WHO: World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Context for this study

Access to medicine for the treatment of illnesses is an essential component of any healthcare system. Many people need to take medication on a daily basis. South Africa's health care system faces many challenges and hence the system struggles to function as optimally as it could (Mayosi, Fisher, Lalloo, Sitas, & Tollman, 2009). The high cost of medicine remains a barrier for most of the South African population (Bangalee, 2015).

One area in health care that has been identified to improve access is the use of generic substitution practices which has been identified as a mechanism that can contain costs (Karim, Pillai, Ziqubu-Page , Cassimjee, & Morar, 1996). This has been supported by legislation that allows for the generic substitution of originator medicines with generic medicines, on condition that the substitution is permitted by the patient (Bangalee, 2015). But, the availability of generic medicines does come with its own set of potential problems which create doubt and a lack of confidence with the use of generic medicines.

This research aims to describe some of the problems that have been identified with the use of generic medicine with a focus on the PIs that are contained in the carton of a generic medicine. The findings of this study provide information that can assist with improving the access and acceptance of generic medicines.

1.1.1 Generic medicines

A generic medicine is defined by the World Health Organization (WHO), as "a pharmaceutical product, usually intended to be interchangeable with an originator product. The generic medicine is manufactured without a license from the originator company and marketed after the expiry date of the patent or other exclusive rights" (Alrasheedy, et al., 2014). While originator medicines must conform to strict safety, quality and efficacy measures prior to obtaining health authority approval, generic

medicines must only prove quality and bioequivalence to the originator medicine. Thus, the requirements for a generic medicine are less stringent than those for the new chemical entity, and the costs of testing and launching a generic medicine are a fraction of research and development costs of originator medicines.

Medicinal products are considered to be bioequivalent if, after they are administered in the same dose, the rate and extent of bioavailability and the effects with respect to safety and efficacy are the same as the originator. There is no need for companies applying for registration of generic medicine to repeat the clinical trial studies that were submitted for registration of the originator medicine. This is one of the reasons why generic medicines are available at a cheaper price than the originator medicine (Dunne, Shannon, Dunne, & Cullen, 2013). Generic medicines have the same active ingredient, dosage form, strength and route of administration as the originator medicine and thus the information gathered is applicable to the generic.

1.1.2 Generic medicine labelling

The primary source of drug information used in South Africa is the approved medicine PI. Generic pharmaceutical companies extract the safety and efficacy information directly from the PI of the originator medicine. Hence the information with respect to safety and efficacy provided in the PI of the generic medicine should be consistent with that provided in the originator medicine PI.

The PI is a document that accompanies a medicine. It is intended to contribute to the safe and efficacious use of a medicine. It includes a scientific explanation of the uses for the medicine and its limitations which has been established by supporting data. It should be written in a manner that is not promotional, false or misleading. The information should be evidence based and updated from time to time as relevant pre-clinical and clinical data becomes available (Deepak, et al., 2013). The PI must be written in a manner that is clear and so that it can be understood by the general population (Al-Ramahi, Zaid, Kettana, Sweileh, & Al-Jabi, 2012).

PIs are used as the primary source of medicine information by both the prescribers and the patient. Sometimes non-compliance in taking medication is because patients misunderstand instructions given by health care professionals. PIs then become a useful tool which conveys the verbal message (Morris & Halperin, 1979). However, some research has shown that PIs may impact patient compliance in an undesirable manner if the information that is provided is unreliable and incomplete (Dutta, Mahato, Saha, & Bhattacharyya, 2014). Incomplete and unreliable information could result in inconsistent prescribing patterns and may have a negative impact on patient safety and overall healthcare (Gharibyar, Sharif, Ghandour, Saffarini, & Aden, 2013).

1.1.3 Approval of Package inserts by the South African Health Authority

Generic medicine can only be registered if it has met all the necessary standards as set out in the guidelines published by the local regulatory body (Sawalha, Sweileh, Zyoud, & Jabi, 2008). These include products that are of a high quality, and that is efficacious and safe for use in the intended population (Alrasheedy, et al., 2014). The South African Health Products Regulatory Authority (SAHPRA), previously known as the Medicines Control Council (MCC) has the task of evaluating and approving the information provided in the package insert (PI). This procedure takes place before the registration of the product. Once the PI has been approved, it cannot be changed unless approval from SAHPRA has been granted.

The Medicines and Related Substances Act (Act no. 101 of 1965) and the general regulations made in terms of the Medicines and Related Substances Act (Act no. 101 of 1965), address the legal requirements that a PI be supplied with every medicine. Regulations 9 and 10 of Act 101 stipulate the minimum information requirements of the PI. Although the type of information provided under specific headings in the PI is mandated by SAHPRA, the process of compiling a PI or amending a PI is not always clear. The regulatory authority plays a key role in determining the contents of the PI however many health authorities, including SAHPRA have challenges that include limited human resources with skills oversight and system insufficiencies (MCC/MRA Backlog Task Team, 2010).

1.2 Literature review

Whilst there has been some research conducted on PIs internationally, very little research has been done in South Africa. International and local research primarily focuses on the differences that have been noted in the various brands of generic medicine PIs (Filby, 2008).

1.2.1 International research

Research that has been conducted internationally shows the following:

The information in PIs is a source of information for patients which contributes to the safe and effective use of the medicine. However, this information is often lacking in consistency, completeness and is sometimes difficult to read and understand. An article published by Shrank and Avorn (2007), explored the potential and limitations of written drug information. Sources of written information available in the United States and the regulations that control the content of information were reviewed. Evidence shows that whilst patients prefer to receive medical information from health care providers, this is not actually what happens. The interaction between health care provider and patient is often inadequate. Patients often do not remember what was discussed and seek written information on how to use their medicine. An observation of medicine labelling showed that there was a lot of variability in the provided consumer medicine information (Shrank & Avorn, 2007).

Prescribing materials from pharmaceuticals of the same drug within even one country was also found to show considerable differences. In 2003, Reggi et al conducted an international comparative study of different brands of the same drug in 26 countries (including America, Europe, Africa, Asia and Australasia). Three widely used drugs were selected: ciprofloxacin, fluoxetine and nifedipine. Results revealed that only two countries reflected all the indications for ciprofloxacin, three countries for fluoxetine and eleven for nifedipine. No countries reflected all the major side effects for nifedipine and fluoxetine and only one country reflected all the side effects for nifedipine. No countries listed all the precautions (Reggi, et al., 2003).

While the indications for a medicine may be different across countries there should be little difference in the listed warnings, precautions and contraindications. However, research has shown that this is not always the case. Pfistermeister et al (2013) conducted an in-depth comparison of the approved German, Swiss, British and US-American prescribing information of the top 10 prescribed psychiatric drugs. The comparison revealed that was a lot of variability in the important information across all the investigated markets. Health care providers who prescribe the same drug for the same medical condition in different countries are presented with different indications, warnings and special precautions or contraindications.

When comparing the current medicine registration system in South Africa to other medicine registration systems in the world it becomes apparent that there are gaps in the current system being used by SAHPRA. The current medicine registration system in South Africa includes the issue of a product registration certificate once the health authority is satisfied that the medicine is proven to be safe, of good quality and is efficacious. The system does not include the provision of any additional public reports that provide information about the considerations that led the regulator to approve or refuse the application. As part of the European Medicines Agency (EMA) and the Therapeutic Goods Administration (TGA) commitment to transparency, public assessment reports are provided upon completion of the review of a medicine (Papathanasiou, et al., 2016). Transparency and communication between the pharmaceutical company and the health authority during the approval process of medicine is crucial.

The EMA guidance documents stipulate specific timelines for evaluation of a medicine application (Kashyap, Gupta, & Ragunandanh, 2013). Currently in South Africa there are no published timelines for registration. The lack of timelines would mean that a medicine could be in the registration process for many years before obtaining approval. This also leads one to believe that there is no accountability on the part of the regulator and that medicines would not be registered as efficiently as they are in other parts of the world. South Africans would thus wait longer to have access to the same medicines that may already be available in other countries.

1.2.2. Local research

Guidelines established by the South African health authority primarily focuses on the structure and content of the information provided under the different headings in the PI. There is very little guidance on the process of compilation that is to be followed and the sources of information to be used for the compilation of a generic medicine PI. The consequence of the lack of prescription in the documents results in regulatory pharmacists having to compile PIs differently using their years of experience in regulatory affairs as a guiding tool.

In South Africa, negative perceptions exist surrounding the use of generic medicines (Patel, Gauld, Norris, & Rades, 2012). Research conducted by Patel et al (2012) explains that the perceptions of health care providers and patient consumers about the quality of generic medicines contributes to a lack in confidence in using them. Mohlala et al (2010) showed that the rate of prescribing drugs by their generic name in public and private health care facilities in 2 provinces in South Africa was as low as 45.2% in the public hospital and 24.5% by GPs (Mohlala, Peltzer, Phaswana-Mafuya, & Ramlagan, 2010). Whilst generic medicines are available in South Africa, patients and health care providers will only use them if they are confident in their safety, efficacy and quality.

Two recent studies were conducted on generic medicine PIs in South Africa (Aziz 2017; Moodley 2016). The study that was carried out in 2016, concluded that PIs of approved products that are currently circulating show considerable differences between the originator product and subsequent generic brands of the same drug substance (Moodley, 2016). Another recent study that was carried out in 2017 evaluated the congruency of information in the patient information leaflet (PIL) as compared to the PI of 6 selected antihypertensive drugs. The study revealed a lack of congruency of key information (Aziz, 2017).

This research adds to the small body of local research and provides insight into the differences noted between the PIs of originator and generic medicines; sources of

information used by regulatory pharmacists, the regulatory process followed and the experiences gained during the compilation of a generic medicine PI for approval by the South African Health Product Regulatory Authority.

1.3 Problem statement

The approval process for generic medicines is set at a lower threshold to enable generic companies to introduce drugs at affordable rates. The PI would be expected to mirror the originator PI as the generic company does not have the obligation to run clinical trials on efficacy and safety. But the timeline for registration in South Africa is long and contributes to a significant delay in access to generic medicines (Bateman, 2010). The processes followed for the compilation, assessment and approval of a generic medicine PI in South Africa is unclear.

Previous research has identified inconsistencies in the information contained in PIs across brands of the same medicines (Pfistermeister, et al., 2013). These create doubt and a lack of confidence regarding the use of generic medicines.

The findings of this study could contribute in assisting SAHPRA to amend and formulate better policies to regulate and approve generic medicine PIs. This will also aid in the better functioning of the pharmaceutical industry's regulatory departments.

1.4 Study aim and Objectives

The aim of the study is to compare the PIs of originator and generic medicines of a small sample of medicines registered in South Africa and to determine the sources of information that are used to compile the generic medicine PI. The study also aims to explain the regulatory process followed by a pharmaceutical company to obtain approval of a generic medicine PI in South Africa.

The objectives of the study are

- To describe the core differences between originator medicine PIs and generic medicine PIs with respect to the listed indications, contraindications, warnings, interactions, dosage and directions for use, side-effects and special precautions.
- To identify the process and the sources of information that regulatory personnel from one pharmaceutical company use to compile the generic medicine PI.
- To explore the experiences and perceptions of the regulatory staff from this pharmaceutical company with regard to compiling generic PIs for approval by SAHPRA.

CHAPTER 2: METHODS

2.1 Introduction

The study was conducted in two phases and a qualitative design was used. Qualitative research methods were used because they enabled the researcher to identify inconsistencies in the PIs through a textual analysis. Qualitative methods were appropriate to identify, describe, and understand the regulatory processes used by pharmacists at a specific pharmaceutical company. The regulatory processes involved in the compilation of a generic medicine PI includes the identification of the sources of information that are used and experiences that were gained during the compilation of a medicine PI. This chapter discusses the methods that were utilized to conduct this study.

2.2 Research site

The pharmaceutical company that was selected as the research site is one of the world's leading generics and specialty pharmaceutical companies. It has products in approximately 140 countries and territories.

The choice of this company as the research site is convenient as the researcher is employed at the pharmaceutical company. The researcher thus has access to the PIs registered by the company in order to conduct the comparative textual analysis. The researcher also has access to the regulatory pharmacists that compiled the PIs in order to conduct focus group discussions about the sources of information used and the regulatory process involved in compiling generic medicine PIs.

2.3 Phases of data collection

There were two phases of data collection. The first was the identification and collection of PIs. Four medicines registered by the pharmaceutical company were identified. This data set was used to compare specific categories of the originator medicine PIs with the corresponding categories of the generic medicine PIs. The data set obtained from the

first phase of data collection was used to address the first objective of the study i.e. To describe the differences between originator medicine PIs and generic medicine PIs with respect to the listed indications, contraindications, warnings, interactions, dosage and directions for use, side-effects and special precautions.

The second phase of data collection was empirical. A focus group discussion was held with six members of the regulatory team employed at the pharmaceutical company. The data set obtained from the second phase of the study was used to address the remaining two objectives of the study; the process that regulatory pharmacists follow for the compilation of a PI, the sources of information that they draw on, and their perceptions and experiences of compiling generic medicine PIs for approval by SAHPRA.

The researcher has ensured trustworthiness of the qualitative research by employing the use of triangulation between the data sets obtained from the different methods used in the study. Triangulation involves the use of different methods which form the major data collection strategies for qualitative research (Shenton, 2004). Triangulation using different methods makes provision for the credibility of the research and also reduces investigator bias thereby making provision for confirmability of the research.

2.4 Data Sets

2.4.1 Package Inserts

Four generic medicines, two hypotensives and two tranquilisers, registered and marketed by the pharmaceutical company were selected and the PIs for these medicines were compared to the corresponding originator brand medicine PI registered in South Africa. The PIs of the selected medicines were sourced from the pharmaceutical company's regulatory affairs folder.

The inclusion criteria for the drug selection were as follows:

a) The generic medicine is currently being marketed in South Africa.

b) The generic medicine was registered by the company in the last 5 years.

The drugs selected for inclusion in the study are shown in Table 1.

Table 1 Selected generic equivalent versus corresponding originator brand, molecule name and pharmacological classification

Originator brand	**Generic equivalent***	**Molecule**	**Pharmacological classification**
Atacand®	GENERIC CANDESARTAN	Candesartan cilexitil	Hypotensive
Micardis®	GENERIC TELMISARTAN	Telmisartan	Hypotensive
Seroquel®	GENERIC QUETIAPINE	Quetiapine fumarate	Tranquiliser
Zyprexa®	GENERIC OLANZAPINE	Olanzapine	Tranquiliser

* The trade names of the generic equivalent have been changed.

Two medicines classified as hypotensives, Candesartan cilexitil and Telmisartan, and two medicines classified as tranquilisers, Quetiapine fumarate and Olanzapine were selected for analysis. These classes of drugs are widely and commonly used in South Africa. Both these classes of medicines are used for the treatment of chronic conditions and contribute to the utilization of a large number of medicines in the South Africa market. Two divergent markets were compared i.e. Cardiovascular and Central Nervous System. Medicines with different pharmacological classifications were selected so that the research would be able to accommodate more than only one category of medicine registered at the company. The results obtained would then be an indication of medicines that were registered across the business and not only to a specific class of medicine.

Specific categories within the PIs were selected for analyses. These are the listed indications, recommended dosage, special precautions, contraindications, side-effects, interactions and warnings. These categories were selected because these sections contain information that are regarded as the most important for the health care provider and the patient (Filby, 2008).

2.4.2 Focus group

A focus group discussion was conducted with the regulatory staff of the company. Focus group discussion is a qualitative research method. This method allows an interviewer to ask study participants specific questions about a topic. This method is an appropriate choice for the research being conducted because it would provide the added dimension of interaction among study participants (Wong, 2008).

Focus group discussions have been criticised for the vulnerability to bias. If there are dominant member/s in the group, it is advised that the interviewer should be aware of how the thoughts and ideas of these group members may influence the group. To deal with this criticism the researcher used the turn-taking approach. This approach ensured that each participant had a turn to contribute to the discussion. The focus group consisted of six participants employed at the company, viz. four registration pharmacists and two regulatory affairs officers. The pharmacists, including the regulatory affairs director, regulatory manager, and officers participating in the focus group, are all actively involved in the direct compilation of generic PIs.

The participants and their qualifications are provided in Table 2. The regulatory staff have been employed at the pharmaceutical company for at least two years and have a lot of experience in the compilation of generic medicine PIs.

Table 2 Participants of the focus group and their qualifications

Name*	Qualification	No. of years employed in regulatory department	Job title
Lynn	Bachelor of Pharmacy, Master of Science in Medicine (Pharmaceutical Affairs)	6	Regulatory Affairs Director and Responsible Pharmacist
Carol	Non-pharmaceutical	10	Regulatory Affairs Manager
Bridget	Bachelor of Pharmacy	3	Regulatory Affairs Pharmacist
Miya	Bachelor of Pharmacy, Master of Science in Medicine (Pharmaceutical Affairs)	5	Senior Regulatory Affairs Pharmacist and Responsible Pharmacist
Tammy	Bachelor of Pharmacy	2	Senior Regulatory Affairs Pharmacist
Thea	Qualified post basic pharmacist assistant	6	Senior Regulatory Affairs Officer

* pseudonyms have been used.

The focus group discussion focused on the following topics (see Appendix B): The results obtained in analysis of the comparison between the originator PI (OPI) and generic PI (GPI); the generic medicines registered by the company; the process followed to register a product, the sources of information used and the experiences the pharmacists had gained over time in the compilation of generic medicine PIs for approval by SAHPRA. The discussions were audio recorded and transcribed to facilitate data analysis.

The focus group discussion was conducted in the boardroom at the pharmaceutical company. The venue was quiet, comfortable and convenient. The focus group participants sat at a table and were able to see and hear one another clearly.

2.5 Ethical considerations

Approval to conduct the study was obtained from the Witwatersrand Human Research Ethics Committee prior to conducting this study (see Appendix C). The researcher obtained permission from the research site. Informed consent was obtained from all the participants of the study.

2.6 Data analysis

2.6.1 Package inserts

A checklist was developed to record the differences in text noted in the selected categories of the generic medicine package and the originator medicine PI (see Appendix A). The following categories contained in the PI were compared and reviewed:

- Indications

- Contraindications

- Warnings

- Interactions

- Dosage and directions for use

- Side-effects

- Special Precautions

A manual comparative textual analysis was conducted on the differences that were noted on the checklist.

2.6.2 Focus group discussion

The audio recorded focus group discussion was transcribed. A thematic content analysis was used to analyze the discussion. Thematic content analysis is a method of data analysis that is used to identify common themes that exist in the text (Burnard, Gill, Stewart, Treasure & Chadwick, 2008).

The results of the textual comparisons were triangulated with the information obtained in the focus group interview.

CHAPTER 3 RESULTS AND DISCUSSION

A generic medicine is expected to provide the same therapeutic effect as the corresponding originator medicine (Dunne, Shannon, Dunne, & Cullen, 2013). Hence the information provided in an originator medicine PI and its corresponding generic medicine package is expected to be the same. The results of this study show that there are considerable differences between the information presented in the PIs. These differences stem from the sources of information that were used to compile the GPI and the regulatory challenges personnel face in obtaining approval of the GPI.

In the context of this research the applicant is the pharmaceutical company that has applied to SAHPRA for registration of a generic medicine.

3.1 Comparative textual analysis of the OPI and GPI

3.1.1 Indications

A comparison of the indications listed in the GPI and OPI of the four selected medicines revealed only one minor difference for one product, GENERIC OLANZAPINE. Table 3 shows that the phrase “in controlled trials” was removed from the indication however the indication for schizophrenia was still listed. The elimination of the words “in controlled trials” was discussed with participants of the focus group. Miya commented that, “the health authority evaluators always remove the reference to clinical trials”. The participants of the focus group believe that the reason for removing the words clinical trials is because clinical trials are not conducted using generic medicines and hence it is incorrect to state this on the GPI even though it is stated on the OPI. The removal of clinical information by the regulatory staff and by the health authority evaluators is of major concern. Generic medicine manufacturers do not repeat the clinical studies that were performed by the originator company and the safety and efficacy profile of the generic medicine should mimic that of the originator medicine as the molecule contained in both medicines is exactly the same. Table 5, 6 and 9 show a similar pattern where clinical and non-clinical information was removed in the PIs of GENERIC OLANZAPINE and GENERIC QUETIAPINE. Upon analysis of the generic PIs that were

evaluated, it is evident that the information on clinical and non-clinical trial information has been removed.

Table 3 Core differences between the OPI and GPI noted under the heading of Indications

Originator Brand	Equivalent generic medicine	No. of differences
Atacand®	GENERIC CANDESARTAN	0
Micardis®	GENERIC TELMISARTAN	0
Seroquel®	GENERIC QUETIAPINE	0
Zyprexa®: - The antipsychotic efficacy of Zyprexa® was established ***in controlled trials*** of schizophrenia in patients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech)	GENERIC OLANZAPINE: - The antipsychotic efficacy of GENERIC OLANZAPINE was established in schizophrenia patients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech)	1

3.1.2 Contraindications

A comparison of the contraindications listed in the GPI and OPI revealed significant differences. Table 4 shows that the GPIs include several important contraindications that have not been listed on the PIs. The GPIs were shown to be more of a comprehensive source of information when compared to the OPIs. Three out of the four medicines had listed additional contraindications in the GPI that were not listed in the OPI.

GENERIC OLANZAPINE was the only medicine whose contraindications matched those in the OPI. For one medicine, GENERIC CANDESARTAN, hepatic impairment was not listed as a contraindication whereas it was stated as a contraindication on the OPI. Another finding in the hypotensive class of medicines was that the limit for

creatinine clearance was stated to be different in the GPIs compared to that stated in the OPIs i.e. 15 ml/min vs 30 ml/min. The implication of these differences is that the OPI would be able to be used in cases where the GPI is contraindicated. The different limits for creatinine clearance would mean that patients who had a creatinine clearance of 15 ml/min would not be able to use the GPI for treatment. However, this should not be possible because the molecule contained in the GPI and the OPI is identical and should be contraindicated in the same group of patients.

The findings were discussed in the focus group and participants noted that it is common for the GPI to have more contraindications as well as more warnings, special precautions, interactions and side-effects than those listed in the OPI. It was agreed among participants that it is common for the GPI to have different limits for creatinine clearance than the limit stated in the OPI. The reason for these differences is because during the process of compiling a GPI, the regulatory staff align the GPI with the latest safety data that is available globally. Tammy explained that it is the company's responsibility to ensure that the GPI provides patients and health care providers with latest safety information even if the OPI does not contain this information. Miya said that, "the company could be sued should the medicine be used in a group of patients where it is contraindicated and the GPI does not mention this as a contraindication". There are a few reasons for the OPI not containing the latest information available globally. It is suggested that the originator company has applied for inclusion of additional contraindications into the OPI and this is under review at the health authority. It is a consideration that the originator company has not applied for inclusion of additional contraindications and the OPI has not been updated after registration was obtained.

Both scenarios are possible. The lengthy evaluation timelines by the health authority may be holding up the update to the OPI since the originator company will not be able to update the OPI unless health authority approval is obtained. On the other hand, the originator company may not have applied for inclusion of the additional contraindications as the health authority does not routinely review the PIs of registered medicines and would not force the originator company to update its PI in line with latest

safety information. Tammy explained that the latter is unlikely because the originator company is obligated to provide patients and health care providers with latest safety information. It is more likely that the originator company has applied for the inclusion of the additional information and has not obtained health authority approval as yet, hence the OPI is not as up to date as the GPI.

These differences highlight a huge risk to patients and health care providers. Health care providers could prescribe the OPI for patients in which the medicine is contraindicated. This could result in patient fatalities.

Table 4 Core differences between the OPI and GPI noted under the heading of Contraindications

Originator Brand	Equivalent generic medicine	No. of differences noted
Atacand®: - Very severely impaired renal function (creatinine clearance < 15 ml/min) - Severely impaired hepatic function	GENERIC CANDESARTAN: - Very severely impaired renal function ***(creatinine clearance < 30 ml/min)*** ***- hepatic impairment was not listed in the GPI – A reduced dosage is recommended*** ***<u>Additional contraindications listed in the GPI:</u>*** - ***Hereditary or idiopathic angioedema*** ***- Renal artery stenosis in patients with a single kidney*** ***- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride*** ***- Porphyria*** ***- Lithium therapy: Concomitant administration may lead to toxic blood concentrations of lithium***	7

Originator Brand	Equivalent generic medicine	No. of differences noted
Micardis®: - Severe renal impairment	GENERIC TELMISARTAN: - Severe renal impairment ***(Creatinine clearance, 30 ml/min)*** ***<u>Additional contraindications listed in the GPI:</u>*** ***- A history of angioedema related to previous therapy with Ace inhibitors or angiotensin receptor blockers (ARB's). Such patients must never be given these medicines.*** ***- Hereditary or idiopathic angioedema*** ***- Hypertrophic obstructive cardiomyopathy (HOCM)*** ***- Bilateral renal artery stenosis*** ***- Renal artery stenosis in patients with a single kidney*** ***- Aortic stenosis*** ***- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride*** ***- Porphyria*** ***- Lithium therapy: Concomitant therapy with*** ***- Generic telmisartan may lead to toxic blood levels of lithium*** ***- Pregnancy and lactation***	12

Originator Brand	Equivalent generic medicine	No. of differences noted
Seroquel®: - Hypersensitivity to any of the components - Pregnancy and lactation, as safety has not been established - Safety and efficacy in children and adolescents have not been demonstrated - Advanced liver and renal function impairment, as safety has not been demonstrated	GENERIC QUETIAPINE: - Hypersensitivity to any of the components - Pregnancy and lactation, as safety has not been established - Safety and efficacy in children and adolescents have not been demonstrated - Advanced liver and renal function impairment, as safety has not been demonstrated ***Additional contraindications listed in the GPI:*** ***- Quetiapine is not indicated for use in elderly patients with dementia exhibiting behavioural disturbance*** ***- Co-administration with azole antifungals, macrolide antibiotics and HIV protease inhibitors***	2
Zyprexa®	GENERIC OLANZAPINE	0

3.1.3 Warnings

A comparison of the warnings listed in the GPI and OPI revealed that three out of the four medicines that were compared showed differences in the warnings that was provided. Table 5 shows that additional warnings were provided in the GPI for two of the medicines i.e. GENERIC CANDESARTAN and GENERIC QUETIAPINE. The Atacand® PI referred the patient to the specific section on pregnancy and lactation for warnings whereas the GPI PI stated the warning for pregnancy under the Warning heading. Thea said that, “this is not an uncommon finding and that the placement of the warning for pregnancy and lactation is dependent upon the health authority evaluator”. Carol

commented that “there is no clear guidance on whether it should be stated under the heading of warnings or under pregnancy in the PI”. What stands out, is the lack in consistency as to where the information appears in the OPI versus where it appears in the GPI. Bridget said that, “it is ideal for patients to be able to refer to either PI and be able to locate the information in the same section rather than to have to find it under a different heading”.

Table 5 shows that the PI for GENERIC QUETIAPINE contained more warnings than that of the corresponding OPI. Again, it can be noted that the GPI is able to provide a more comprehensive list of warnings for the medicine. Tammy commented that “the additional warnings have been included in line with the latest originator medicine PI that was registered and approved overseas”.

The PI for GENERIC OLANZAPINE revealed that non-clinical data was removed in the GPI. Participants in the focus group explained that the removal of non-clinical data is requested by the SAHPRA evaluators because the registration of generic medicines do not require non-clinical studies to be submitted for evaluation and approval and that even though it is present in the OPI, it must be removed in the GPI. Non-clinical trials are performed to determine the pharmacokinetics, pharmacodynamics and safety profile of the drug. Non-clinical safety assessments are done by utilizing animal toxicological studies. The data from these studies are used to determine if there could be any potential safety risk when used in humans (TM, 2015). The information obtained during non - clinical trials determine the viability of progressing with further trials on the drug. Regulatory authorities across the world require non-clinical data prior to registration of an innovator medicine (Umscheid, Margolis, & Grossman, 2011). It is interesting to note that the originator company felt that this information was important enough to include into the OPI however this was removed in the GPI. The data obtained during non-clinical studies using originator drugs are applicable to generic medicines and should be included into the GPI. The registration of a generic medicine does not require clinical studies to be performed because they were already carried out using the originator medicine which contains the same active molecule. Hence the safety profile of the originator medicine is applicable to that of the generic medicine.

Table 5 Core differences between the OPI and GPI noted under the heading of Warnings

Originator Brand	Equivalent generic medicine	No. of differences noted
Atacand®: - Refer to pregnancy and lactation for warnings	GENERIC CANDESARTAN: ***<u>Warning listed in the GPI:</u>*** ***Should a woman become pregnant while receiving GENERIC CANDESARTAN, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine***	1
Micardis®	GENERIC TELMISARTAN	0
Seroquel® - Hyperglycaemia and diabetes mellitus: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. - Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics such as Seroquel, should be monitored regularly for worsening of glucose control. - Patients with risk factors for diabetes mellitus who are starting on treatment with atypical antipsychotics as Seroquel, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness.	GENERIC QUETIAPINE: - Hyperglycaemia and diabetes mellitus: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including GENERIC QUETIAPINE. - Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics such as GENERIC QUETIAPINE, should be monitored regularly for worsening of glucose control. - Patients with risk factors for diabetes mellitus who are starting on treatment with atypical antipsychotics as GENERIC QUETIAPINE, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness.	4

Originator Brand	Equivalent generic medicine	No. of differences noted
- Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as Seroquel, should undergo fasting blood glucose testing. - In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as Seroquel, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of suspect drug.	- Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as GENERIC QUETIAPINE, should undergo fasting blood glucose testing. - In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as GENERIC QUETIAPINE, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of suspect drug. ***<u>Additional warnings listed in the GPI:</u>*** ***- Where the use of GENERIC QUETIAPINE in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances, over sedation and complications associated with hyperglycaemia. Before prescribing GENERIC QUETIAPINE clinicians are advised to carefully assess the risks and benefits of the use of GENERIC QUETIAPINE in elderly patients with dementia as there has been an increase in the cerebrovascular events. In these cases, the risk prediction for stroke in the individual patient must be taken into account.***	

Originator Brand	Equivalent generic medicine	No. of differences noted
	- GENERIC QUETIAPINE must be used in caution in patients with known cardiovascular disease or other conditions predisposing to hypotension ***- GENERIC QUETIAPINE must be discontinued if signs and symptoms of tardive dyskinesia appear*** ***- GENERIC QUETIAPINE must be discontinued and appropriate medical treatment given in case of neuroleptic malignant syndrome***	
Zyprexa®: - Hyperprolactinaemia: Zyprexa® elevates prolactin levels and a modest elevation persists during chronic administration. ***An increase in mammary gland neoplasms has been found in rodents after chronic administration of antipsychotic medicines and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumours in rodents is unknown.***	GENERIC OLANZAPINE: - Hyperprolactinaemia: GENERIC OLANZAPINE elevates prolactin levels and a modest elevation persists during chronic administration.	1

3.1.4 Interactions

A comparison of the interactions listed in the GPI and OPI revealed that all four medicines showed differences in the interactions that were listed. Miya explained that the global pharmacovigilance systems offer a platform for suspected interactions between medicines to be reported and investigated. The reporting of the suspected interactions happens after the registration of a medicine. The PI that is available globally

would be updated in line with latest information that has been obtained from the global pharmacovigilance systems. This could be a reason why the interactions listed in the local OPI and the GPI are different. This difference could also be noted in the side-effects section of the PI. The WHO explains pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Pharmacovigilance has been expressed as a key component for effective drug regulation and has been cited as the worldwide master key for drug safety monitoring (Jeetu & Anusha, 2010).

Miya commented that, “all generic companies have a pharmacovigilance department that record and investigate any adverse events that are reported by health care providers and patients”. Often when an originator medicine becomes available on the market, only the interactions discovered during clinical trials are listed in the PI because these are the only known interactions that exist. When patients begin taking the medicine additional interactions are noted and can be picked by pharmacovigilance systems or post marketing studies. Miya thought that it was possible that the originator company may have applied for the local OPI to be updated but that, these changes may still be undergoing evaluation at the health authority level.

Table 6 shows that the PI for GENERIC CANDESARTAN states the following, “Post marketing reports suggest a rare but significant interaction with increase of INR and bleeding with concomitant warfarin therapy “. This is an additional interaction between the concomitant use of warfarin and candesartan cilexitil. Although the OPI states that warfarin was investigated during clinical pharmacokinetic studies it does state that the concomitant use of these medicines leads to an increase in INR (International Normalised Ratio) and bleeding. This is a significant interaction and was listed in the GPI only. This data was derived from post marketing reports and included into the GPI by the regulatory affairs pharmacist that was compiling the GPI.

Table 6 shows that an additional interaction listed for GENERIC TELMISARTAN was not listed in the OPI. The GPI stated that the concomitant treatment of telmisartan with non-steroidal anti-inflammatory drugs (NSAIDS) is associated with the potential for

acute renal insufficiency in patients who are dehydrated and that patients receiving NSAIDS concomitantly with telmisartan need to be adequately hydrated. Health care providers who prescribe the OPI may not be aware of this interaction and could prescribe GENERIC CANDESARTAN for a patient who is not adequately hydrated and the patient would be at risk of developing renal problems. NSAIDs are very commonly used by patients and can be obtained as over the counter preparations at pharmacies.

The PI for Seroquel® stated that the dose of Quetiapine would have to be reduced when taken with potent CYP34A inhibitors such as antifungals and macrolide antibiotics however the GPI stated that concomitant use of quetiapine and potent CYP34A inhibitors such as HIV protease inhibitors, azole antifungals and macrolide antibiotics were contraindicated. This finding is important because it illustrates that the GPI not only advises that the concomitant use of quetiapine and potent CYP34A inhibitors is contraindicated but it also provides more specific examples of CYP34A inhibitors. Human immunodeficiency virus (HIV) is very prevalent in South African and hence the inclusion of this information is vital. The GPI is also specific in noting the class of antifungals as azole antifungals whereas the OPI fails to do so. Again, the comparison of information between the OPI and GPI shows that the GPIs contained more comprehensive information.

Table 6 shows the removal of statistical clinical trial information in the PI of GENERIC OLANZAPINE. The removal of clinical trial information was also noted in Table 1.

Table 6 Core differences between the OPI and GPI noted under the heading of Interactions

Originator Brand	Equivalent generic medicine	No. of differences noted
Atacand®: - No interactions of clinical significance have been identified - Compounds which have been investigated in clinical pharmacokinetic	GENERIC CANDESARTAN: - No interactions of clinical significance have been identified - Compounds which have been investigated in clinical pharmacokinetic	1

Originator Brand	Equivalent generic medicine	No. of differences noted
studies include hydrochlorothiazide, ***warfarin***, digoxin, oral contraceptives, glibenclamide, nifedipine and enalapril - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with Atacand and careful monitoring of serum lithium levels is recommended during concomitant use. - The antihypertensive effect of Atacand may be enhanced by other antihypertensives. - The bioavailability of candesartan is not affected by food.	studies include hydrochlorothiazide, digoxin, oral contraceptives, glibenclamide and nifedipine and enalapril - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with GENERIC CANDESARTAN and careful monitoring of serum lithium levels is recommended during concomitant use. - The antihypertensive effect of Atacand may be enhanced by other antihypertensives. - The bioavailability of candesartan is not affected by food. ***<u>Additional interaction listed in the GPI:</u>*** ***Post marketing reports suggest a rare but significant interaction with increase of INR and bleeding with concomitant warfarin therapy***	
Micardis®: - May increase the hypotensive effect of other antihypertensive agents - Compounds which have been studied in pharmacokinetic trials include digoxin, warfarin, HCTZ, glibenclamide, paracetamol, ibuprofen, simvastatin and amlodipine - For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (in a single case a	GENERIC TELMISARTAN: - May increase the hypotensive effect of other antihypertensive agents - Compounds which have been studied in pharmacokinetic trials include digoxin, warfarin, HCTZ, glibenclamide, paracetamol, ibuprofen, simvastatin and amlodipine - For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (in a single case a	1

Originator Brand	Equivalent generic medicine	No. of differences noted
39%), monitoring of plasma digoxin levels should be considered - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with Micardis. - Careful monitoring of serum lithium levels is recommended during concomitant use.	39%), monitoring of plasma digoxin levels should be considered - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with Micardis. - Careful monitoring of serum lithium levels is recommended during concomitant use. ***Additional interactions listed in the GPI:*** ***Concomitant treatment with NSAIDS (including aspirin at anti-inflammatory dosage regimens. COX-2 inhibitors and non-selective NSAIDS) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin-angiotensin-system, like GENERIC TELMISARTAN, may have synergistic effects. Patients receiving NSAIDs and GENERIC TELMISARTAN should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. A reduced effect of antihypertensive medicines, like GENERIC TELMISARTAN, by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDS***	

Originator Brand	Equivalent generic medicine	No. of differences noted
Seroquel®: - In a multiple dose trial in healthy volunteers to assess the pharmacokinetics of Seroquel given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of Seroquel of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half life of Seroquel increased from 2,6 to 6,8 hours, but the mean t_{max} was unchanged. ***Due to the potential for an interaction of similar magnitude in a clinical setting, the dosage of Seroquel should be reduced during concomitant use of Seroquel and potent CYP34A inhibitors (such as antifungals and macrolide antibiotics)***	GENERIC QUETIAPINE: - The co-administration of ketoconazole and GENERIC QUETIAPINE may result in a significant (5-fold) increase in the AUC of GENERIC QUETIAPINE. On the basis of this, ***concomitant use of GENERIC QUETIAPINE and potent CYP34A inhibitors, such as HIV protease inhibitors, azole antifungals and macrolide antibiotics, is contraindicated.*** ***<u>Additional interactions listed in the GPI:</u>*** ***- GENERIC QUETIAPINE should be used in caution in patients also receiving antihypertensives or medicines that prolong the QT interval*** ***- GENERIC QUETIAPINE may antagonize the actions of dopaminergics, such as levodopa***	3
Zyprexa®: ***- In clinical trials with oral administration, olanzapine was not associated with a persistent increase in absolute QTC intervals. Only 8 of the 1685 subjects had increased QTc interval on multiple occasions.*** However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients	GENERIC OLANZAPINE: - As with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients when congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesemia.	1

Originator Brand	Equivalent generic medicine	No. of differences noted
when congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesemia.		

3.1.5 Dosage and directions for use

A comparison of the dosage and directions for use listed in the GPI and OPI revealed that only two medicines showed differences in the dosage and directions for use. Table 7 shows that GENERIC CANDESARTAN was contraindicated in patients with impaired renal function whereas the OPI advised using a lower dose of 4 mg. It is interesting to note that in Table 7 the OPI states that in patients with more severe renal impairment (i.e. creatinine clearance < 15 – 30 ml/min/1.73 m^2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be used however in Table 4 it lists severely impaired renal function as a contraindication. The normal corrected GFR is 80–120 mL/min/1.73m2, impaired renal function is 30–80 mL/min/1.73m2 and renal failure is less than 30 mL/min/1.73m2 (Nankivell, 2001). The information provided in the OPI is not consistent within the different sections of the OPI.

An additional statement was included into the dosage and directions for use of GENERIC OLANZAPINE. Tammy said that, “this data is included in line with latest safety data”.

The SAHPRA guidelines emphasize that the dosage and directions for use of the OPI and GPI should be the same. The WHO defines a generic medicine as a pharmaceutical product which is interchangeable with the originator brand product. Health care professionals will therefore prescribe and use the generic medicine in the same way as the originator product. Should the dosage and directions for use be different, this will have major consequences for treatment. A generic manufacturing

company has the responsibility of ensuring that the information provided in the GPI is the same as that of the information provided in the PI of the originator medicine (Narang, 2016). The identical dosage and directions for use between the GPI and OPI would allow physicians to use the generic medicine with confidence. If the information provided under this section is different then it leads one to question whether the generic medicine is truly interchangeable with the originator brand product. As previously explained it is possible that the originator company may have applied for these changes to be made in the local OPI and these may still be under evaluation at the health authority.

Table 7 Core differences between the OPI and GPI noted under the heading of Dosage and Directions for use

Originator Brand	Equivalent generic medicine	No. of differences noted
Atacand®: - Use in impaired renal function: No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 ml/min/1.73 m^2 BSA). ***In patients with more severe renal impairment (i.e. creatinine clearance < 15 – 30 ml/min/1.73 m^2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be used.***	GENERIC CANDESARTAN: - Use in impaired renal function: No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 ml/min/1.73 m^2 BSA). ***In patients with more severe renal impairment (i.e. creatinine clearance < 30 ml/min/1.73 m^2 BSA), GENERIC CANDESARTAN is contraindicated.***	1
Micardis®	GENERIC TELMISARTAN	0
Seroquel®	GENERIC QUETIAPINE	0

Originator Brand	Equivalent generic medicine	No. of differences noted
Zyprexa®: - Psychotic disorders: Zyprexa® tablets should be administered on a once a day schedule without regards to meals, generally beginning with an initial dose of 5 to 10 mg/day, with a target dose of 10 mg/day within several days - In order to evaluate efficacy and guard against side-effects, dosage increases should not be considered before one week, since steady state for olanzapine would not be achieved for approximately one week. The dose range is from 5 mg to 20 mg per day. Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment - Acute mania in bipolar disorder: initial dose: Zyprexa® should be administered on a once a day schedule without regard to meals, generally beginning with 10 mg. Dosage adjustments within the dose range of 5 mg to 20 mg, if indicated, should not occur at intervals of not less than 24 hours. - Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg per day. For patients who have been receiving Zyprexa® for	GENERIC OLANZAPINE: - Psychotic disorders: GENERIC OLANZAPINE tablets should be administered on a once a day schedule without regards to meals, generally beginning with an initial dose of 5 to 10 mg/day, with a target dose of 10 mg/day within several days - In order to evaluate efficacy and guard against side-effects, dosage increases should not be considered before one week, since steady state for olanzapine would not be achieved for approximately one week. The dose range is from 5 mg to 20 mg per day. Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment - Acute mania in bipolar disorder: initial dose: GENERIC OLANZAPINE should be administered on a once a day schedule without regard to meals, generally beginning with 10 mg. Dosage adjustments within the dose range of 5 mg to 20 mg, if indicated, should not occur at intervals of not less than 24 hours. - Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg per day. For patients who have been receiving GENERIC OLANZAPINE for	1

Originator Brand	Equivalent generic medicine	No. of differences noted
treatment of manic episode, continue therapy for preventing reoccurrence at the same dose. An increase to a greater dose than the recommended starting dose, within the range of 5 mg to 20 mg per day, is advised only after appropriate clinical assessment and should generally occur at intervals of not less than 24 hours. The safety of doses above 20 mg/day has not been evaluated in clinical trials. Gradual tapering of the dose should be considered when discontinuing Zyprexa®.	treatment of manic episode, continue therapy for preventing reoccurrence at the same dose. An increase to a greater dose than the recommended starting dose, within the range of 5 mg to 20 mg per day, is advised only after appropriate clinical assessment and should generally occur at intervals of not less than 24 hours. The safety of doses above 20 mg/day has not been evaluated in clinical trials. Gradual tapering of the dose should be considered when discontinuing GENERIC OLANZAPINE. ***<u>Additional dosage and directions for use listed in the GPI:</u>*** ***Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment. A 5 mg starting dose should be considered for patients with hepatic impairment and may also be considered for the elderly patient. The safety of doses above 20 mg/day has not been evaluated in clinical trials. Improvement in the patient's clinical condition may take several days to weeks. Patients should be closely monitored during this period.***	

3.1.6 Side-effects

A comparison of the side-effects listed in the GPI and OPI revealed that all four medicines showed differences in the side-effects that were listed. Many additional side-

effects were included into the GPI. Miya said that, “this finding is expected and that pharmacovigilance systems contribute to the inclusion of the additional side-effects”.

The frequency of the side-effects is mentioned in all of the generic PIs where they may previously not have been mentioned in the OPI. The side-effect listed in the GPI would be classified under a different heading as compared to the heading in the OPI. Table 8 shows that in the PI of Atacand® angio-oedema was listed as a side effect under the heading skin and subcutaneous tissue disorders with no indication of frequency whereas it is listed on the GPI as an Immune system disorder as less frequent: Angioedema. Miya explained that this is not uncommon and that generic medicine PIs may reflect a frequency and heading that is listed in line with data in the overseas OPI. At the time of compiling a generic medicine PI the regulatory staff would use the latest available information from available reference sources to classify the heading and include the frequency of the side-effect. Tammy said that the, “additional side-effects present in the overseas OPI is also included at the same time”.

The comparison of the side-effects listed in Table 8 showed that the GPIs had a more extensive side-effect profile. The PI for GENERIC QUETIAPINE showed many differences to the OPI Zyprexa®. The body system category under which the side-effect was listed was very different to the OPI. There were many additional side effects listed under each of the headings. For example, in Table 8, the OPI Zyprexa® stated under the body system musculoskeletal, side-effect: rhabdomyolysis. In the GPI, this was stated under the body system musculoskeletal, connective tissue and bone disorders, side effect: less frequent: Extremity pain, join paint, back pain, rhabdomyolysis.

Patients who may be switched from the originator medicine to the generic medicine might be hesitant to use the generic medicine as they may believe that generic medicine causes more side effects and is less safe than the originator medicine because it causes more side effects.

Table 8 Core differences between the OPI and GPI noted under the heading of Side-effects

Originator Brand	Equivalent generic medicine	No. of differences noted
Atacand®: - Skin and subcutaneous tissue disorders: ***Angio-oedema***, rash, uticaria, pruritic - Musculosketal, connective tissue and bone disorders: Back pain	GENERIC CANDESARTAN: - Skin and subcutaneous tissue disorders: rash, uticaria, pruritic ***<u>Additional side-effects listed in the GPI:</u>-*** ***The most frequently reported adverse reactions were hyperkalaemia, hypotension and renal impairment. These events were more frequent in patients over 70 years of age, diabetics or subjects who received other medicinal products.*** **-** Musculosketal, connective tissue and bone disorders: Less frequent: Back pain, ***Arthralgia and myalgia*** - ***Immune system disorders:*** ***Less frequent: Angioedema*** ***- Gastrointestinal disorders:*** ***Less frequent: Nausea***	4

Originator Brand	Equivalent generic medicine	No. of differences noted
Micardis®: - Infections and infestations: Common: Urinary tract infections (UTI), upper respiratory tract infections. - Blood and the lymphatic systemic disorders: Rare: eosinophilia, thrombocytopenia - Nervous system disorders: Rare: faintness - Vascular disorders Rare: hypotension - Respiratory, thoracic and mediastinal disorders: - Skin and subcutaneous tissue disorders: Common: eczema Uncommon: increased sweating Rare: erythema, pruritis, angio-oedema, urticaria - Musculoskeletal, connective tissue and bone disorders:	GENERIC TELMISARTAN: - Infections and infestations: ***Less frequent:*** ***UTI including cystitis, upper respiratory tract infection including pharyngitis and sinusitis, sepsis including fatal outcome*** - Blood and the lymphatic systemic disorders: Less frequent: eosinophilia, thrombocytopenia ***Less frequent: Anaemia and neutropenia*** - Nervous system disorders: Less frequent: faintness, ***Somnolence, headache, dizziness, fatigue*** - Vascular disorders Rare: hypotension, ***orthostatic hypotension*** - Respiratory, thoracic and mediastinal disorders: Less frequent: dyspnoea, ***cough, interstitial lung disease*** - Skin and subcutaneous tissue disorders: ***Less frequent:*** eczema***,*** increased sweating, erythema***,*** pruritis, uticaria***, drug eruption, toxic skin eruption, rash*** - Musculoskeletal, connective tissue and bone disorders:	14

Originator Brand	Equivalent generic medicine	No. of differences noted
Common: arthralgia, myalgia, back pain, cramps in legs or leg pain Uncommon: tendinitis like symptoms Rare: ***weakness*** - General disorders and administration site conditions: Common: chest pain, influenza-like symptoms ***Rare: lack of efficacy***	Less frequent: back pain, muscle spasms, myalgia, arthralgia, pain in extremity, tendon pain - General disorders and administration site conditions: Less frequent: chest pain, influenza-like symptoms, ***weakness*** ***<u>Additional side-effects listed in GPI:</u>*** ***- Anaphylactic reaction, hypersensitivity, angioedema*** ***- Abnormal hepatic function/liver disorder*** ***- Renal impairment, including acute renal failure*** ***- Sepsis: An increased incidence of sepsis has been reported with telmisartan compared*** **with placebo** ***Hypotension*** ***- Abnormal hepatic function/ liver disorder: Most cases of abdominal hepatic function/ liver disorder occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions*** ***- Interstitial lung disease: Cases of interstitial lung disease have been reported in temporal association with the intake of GENERIC TELMISARTAN***	

Originator Brand	Equivalent generic medicine	No. of differences noted
Seroquel®: - Nervous system disorders: Dizziness, somnolence, Syncope Seizures - Blood and lymphatic system disorders: Leucopenia, Eosinophilia, Neutropenia - General disorders and administration site conditions: Asthenia, peripheral oedema ***Neuroleptic malignant syndrome*** - Vascular disorders: Orthostatic hypotension - Immune system disorders: Hypersensitivity (angioedema, anaphylaxis, uticaria/rash) - Reproductive system and breast disorders: Priaprism	GENERIC QUETIAPINE: - Nervous system disorders: ***Frequent:*** Dizziness, somnolence, ***headache, anxiety, syncope, extrapyramidal symptoms*** ***Less frequent:*** Seizures, ***neuroleptic malignant syndrome, tardive dyskinesia.*** - Blood and lymphatic system disorders: ***Frequent:*** Leucopenia ***Less frequent:*** Eosinophilia, Neutropenia, ***Thrombocytopenia*** ***Reported but frequency unknown: Agranulocytosis*** - General disorders and administration site conditions: Asthenia, peripheral oedema***, withdrawal symptoms*** - Vascular disorders: ***Frequent:*** Orthostatic hypotension ***Less frequent: Venous thromboembolism*** - Immune system disorders: Hypersensitivity (angioedema, anaphylaxis, uticaria/rash), ***Steven-Johnson syndrome*** - Reproductive system and breast disorders: Priaprism, ***galactorrhoea***	10

Originator Brand	Equivalent generic medicine	No. of differences noted
	<u>Additional side-effects listed in the GPI:</u> ***- Metabolism and nutritional disorder:*** ***Less frequent: Hyperglycaemia, diabetes mellitus*** ***- Psychiatric disorders: Frequent:*** ***Abnormal dreams, nightmares*** ***- Hepatobiliary disorders: Less frequent:*** ***Jaundice, hepatitis*** ***- Eye disorders: Reported but frequency unknown: asymptomatic changes in the lens of the eye with long-term treatment, blurred vision***	
Zyprexa®: - Metabolic: Diabetic coma, Diabetic ketoacidosis, Hypercholesterolaemia, Hyperglycaemia, Hypertriglycericaemia Peripheral oedema - Musculoskeletal: Rhabdomyolysis - Urogenital system: Very rare: Priapism	GENERIC OLANZAPINE: ***- Metabolic and nutritional disorders***: Frequent: Weight gain, increased appetite Less frequent: Diabetic coma, Diabetic ketoacidosis, Hyperglycaemia, Hypertriglycericaemia, ***development or exacerbation of diabetes*** ***- Musculoskeletal, connective tissue and bone disorders:*** ***Less frequent: Extremity pain, joint pain, back pain,*** rhabdomyolysis ***- Reproductive system and breast disorders:*** ***Frequency unknown:*** Priapism, **menstrual syndrome**	14

Originator Brand	Equivalent generic medicine	No. of differences noted
- Skin and appendages: Rare: Rash - Hematology Common: Eosinophilia - Respiratory system: Pneumonia	***- Skin and subcutaneous disorders:*** ***Less frequent: photosensitivity disorders,*** ***Frequency unknown:*** rash**,** ***alopecia*** ***- Blood and lymphatic system disorders:*** ***Frequent:*** Eosinophilia***, leucopenia, thrombocytopenia, neutropenia*** ***- Respiratory, thoracic and mediastinal disorders: Frequent:*** Pneumonia ***Less frequent: rhinitis, cough, pharyngitis*** ***<u>Additional side-effects listed in the GPI:</u>*** ***- Psychiatric disorders: Less frequent: personality disorder, amnesia, anxiety, euphoria, hostility*** ***- Nervous system disorder: Frequent: headache, agitation, nervousness, myoclonus, extrapyramidal effects, dystonia*** ***Less frequent: dyskinesia, movement disorder, articulation impairment, hypertonia, neuroleptic malignant syndrome, tardive dyskinesia*** ***- Eye disorders: less frequent: Amblyopia, blepharitis, corneal lesion*** ***- Cardiac disorders: Less frequent: Chest pain, tachycardia, changes in ECG parameters, ventricular tachydysrhythmias*** ***- Vascular disorders: Frequent: hypotension, peripheral odema*** ***- Gastrointestinal disorders: Frequent: abdominal pain***	

Originator Brand	Equivalent generic medicine	No. of differences noted
	- General disorders and administration site conditions: Frequency unknown: Fever, intentional injury ***- Investigations: high creatine phosphokinase, decreased erythrocyte count, hematocrit, haemoglobin, leucocyte count, lymphocytes, thrombocytes and platelets, increased MCHC, monocytes and eosinophils, decreased bicarbonate, calcium phosphorous, albumin and total protein, increased chloride, GGT and phosphorous***	

3.1.7 Special precautions

A comparison of the special precautions listed in the GPI and OPI revealed that all medicines showed differences in the special precautions that were listed. Table 9 shows that additional special precautions were listed in the GPI of GENERIC QUETIAPINE and GENERIC OLANZAPINE. Bridget said that, “the special precautions in the GPI are aligned to global safety data available in the overseas OPI that is used when compiling the local GPI”.

In the hypotensive group of medicines, the generic medicine was contraindicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy**.** The OPIs had listed this as a special precaution and not as a contraindication. Another significant finding for GENERIC TELMISARTAN was that concomitant use of potassium sparing diuretics and GENERIC TELMISARTAN was not recommended whereas the OPI advised that potassium sparing diuretics should be used in caution with the originator medicine.

This conflicting information means that the originator medicine could be used cautiously whilst the generic medicine is contraindicated. This should not be possible because the molecule contained in both the generic and originator medicine is the same and the information provided in the OPI and GPI should be identical. It is well known that generic medicines contain the same active pharmaceutical ingredient (API) as that of the corresponding originator medicine. The API is responsible for having the desired biological effect (Gavura, 2012). This means that the since the active ingredient is the same in both the originator and generic medicines, both medicines should behave in the same way and result in the same desired effect. The inconsistency in the provision of information compromises health care providers and patients.

Table 9 shows that withdrawal information was included into the PI of GENERIC QUETIAPINE. This information is useful when patients no longer require treatment. The OPI fails to provide such information. The medicine should be gradually withdrawn otherwise the patient could experience withdrawal symptoms.

The OPI for olanzapine stated that blood pressure should be periodically measured in patients over 65 years of age because postural hypotension was infrequently observed during clinical trials. Table 9 shows that this information was removed in the GPI. Non-clinical information on carcinogens, mutagenesis and fertility was also removed in the GPI. The participants of the focus group explained that the removal of non-clinical information was requested by the health authority evaluator as the clinical trial was not conducted using the generic medicine. Generic medicine applications piggy back on the studies that were performed by originator companies and hence do not have to perform their own clinical studies (Dunne, Shannon, Dunne, & Cullen, 2013). For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product (Hari Das, Prasant, Steffi, & Naushad, 2013). Bioequivalence testing links the generic medicine to the clinical studies that were conducted by the originator drug. The clinical studies performed on originator hence become applicable to the generic medicine as well and should be included in the GPI. Non-clinical trials are performed to determine the pharmacokinetics, pharmacodynamics and safety profile of

the drug. Non-clinical safety assessments are done by utilizing animal toxicological studies. The data from these studies are used to determine if there could be any potential safety risk when used in humans (TM, 2015). The data obtained during non-clinical studies using originator drugs are applicable to generic medicines and should be included into the GPI. Additional Information on plasma clearance in smokers and on lipids alterations was provided in the GPI. The removal of some information and addition of other information in the GPI showed a lack in consistency between the information presented in the GPI and the OPI.

The special precautions listed for sorbitol, lactose and soya lecithin is important for patients who have an intolerance towards these excipients. The excipients contained in generic medicines may differ to those that have been used to manufacture originator medicines. This would explain why the special precaution does not appear on both the OPI and GPI. The excipients contained in the originator medicine has not been listed on the OPI and hence it is not known whether the originator medicine contains soya lecithin or lactose. The current SAHPRA guidelines state that the excipients contained in medicines must be listed on the PI. The fact that the excipients were not listed on the local OPI indicates that it had not been updated in line with current SAHPRA guidelines.

Table 9 Core differences between the OPI and GPI noted under the heading of Special Precautions

Originator Brand	Equivalent generic medicine	Total no. of differences noted
Atacand®: - Aortic and mitral valve stenosis: Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy	GENERIC CANDESARTAN: - ***GENERIC CANDESARTAN is contraindicated*** in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy	1

Originator Brand	Equivalent generic medicine	Total no. of differences noted
Micardis®: - Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy**.** **-** Hyperkalaemia: During treatment with other medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-***administered cautiously with Micardis*** - Sorbitol: Micardis tablets contains sorbitol and is therefore unsuitable for patients with hereditary fructose intolerance	GENERIC TELMISARTAN: ***- GENERIC TELMISARTAN is contraindicated*** in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy**.** **-** Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore ***not be co-administered with GENERIC TELMISARTAN*** ***- Sorbitol special precaution was not listed in the GPI***	3

Originator Brand	Equivalent generic medicine	Total no. of differences noted
Seroquel®: - ***In clinical trials Seroquel was not associated with a persistent increase in QTc intervals.*** However, caution should be exercised when Seroquel is prescribed with drugs known to prolong QTc interval, especially in the elderly. - Effect on ability to drive and use machines: Seroquel may cause somnolence which may interfere with activities requiring mental alertness. Patients should be advised not to operate hazardous machines, or drive vehicles, until individual susceptibility is known.	GENERIC QUETIAPINE: Caution should be exercised when GENERIC QUETIAPINE is prescribed with drugs known to prolong QTc interval, especially in the elderly. - Effect on ability to drive and use machines: GENERIC QUETIAPINE may cause somnolence which may interfere with activities requiring mental alertness. Patients should be advised not to operate hazardous machines, or drive vehicles, until individual susceptibility is known. ***Withdrawal recommendation: It is recommended that GENERIC QUETIAPINE be gradually withdrawn because of the risk of withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses with abrupt cessation. Recurrence of psychotic symptoms may also occur and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesis) have been reported.*** ***<u>Additional special precaution listed in the GPI:</u>*** ***- Lactose: GENERIC QUETIAPINE contains lactose. Patients with hereditary galactose intolerance, the Lapp lactase deficiency or glucose-galactose***	2

Originator Brand	Equivalent generic medicine	Total no. of differences noted
	malabsorption should not take GENERIC QUETIAPINE	
Zyprexa®: - Geriatric use: In clinical studies, in general, there was no indication of any different tolerability of Zyprexa® in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to Zyprexa®, should lead to consideration of a lower starting dose. ***As postural hypotension was infrequently observed in the elderly in clinical trials, it is recommended that blood pressure is measures periodically in patients over 65 years***. - Orthostatic hypotension: Zyprexa® may induce orthostatic hypotension associated dizziness, tachycardia and in patients, syncope, especially during initial treatment period.	GENERIC OLANZAPINE: - Geriatric use: In clinical studies, in general, there was no indication of any different tolerability of GENERIC OLANZAPINE in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to GENERIC OLANZAPINE, should lead to consideration of a lower starting dose. - Orthostatic hypotension: GENERIC OLANZAPINE may induce orthostatic hypotension associated dizziness, tachycardia and in patients, syncope, especially during initial treatment period. ***Plasma clearance of olanzapine is higher in smokers. The combined effects of age, smoking and gender could lead to substantial pharmacokinetic differences. The clearance in young smoking males, for example, may be 3 times higher than that in elderly non-smoking females. Dosing modification may be necessary in patients who exhibit a combination of***	7

Originator Brand	Equivalent generic medicine	Total no. of differences noted
	factors that may result in slower metabolism of olanzapine	
- Haematology: Caution should be exercised when using olanzapine in the following types of patients: - Low leucocyte and/or neutrophil counts due to any reason - History of medicine induced bone marrow depression/toxicity - bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy - Hypereosinophilic conditions or with myeloproliferative disease ***Thirty-two patients with clozapine-related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts.***	- Haematology: Caution should be exercised when using olanzapine in the following types of patients: - Low leucocyte and/or neutrophil counts due to any reason - History of medicine induced bone marrow depression/toxicity - bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy - Hypereosinophilic conditions or with myeloproliferative disease	
- Carcinogens: Based on the results of studies in mice and rats it was concluded that olanzapine is not carcinogenic. - Mutagenesis: Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and in vitro and in vivo mammalian tests.	***- Information on carcinogens removed from the GPI*** ***- Information on mutagenesis removed from the GPI***	

Originator Brand	Equivalent generic medicine	Total no. of differences noted
- Impairment of fertility: In rats, male mating, but not fertility, was impaired. Discontinuation of olanzapine treatment reversed the effect on mating performance. In female rats, oestrus cycles and reproduction parameters were influenced at doses higher than the maximum human dose.	***- Information on fertility removed from the GPI*** ***<u>Additional special precautions listed in the GPI:</u>*** ***- Lipid alterations: Undesirable alterations in lipids have been observed in patients with low leucocyte and/or neutrophil counts due to any reason, patients with a history of medicine-induced bone marrow depression/toxicity, patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy, and in patients with hypereosinophilic conditions or with myeloproliferative disease*** ***- Lactose: GENERIC OLANZAPINE tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take GENERIC OLANZAPINE.*** ***- Lecithin soya: GENERIC OLANZAPINE tablets contain lecithin soya. Patients who are allergic to peanut or soya, should not take GENERIC OLANZAPINE.***	

3.2 Summary of the textual analysis (First data set)

The comparisons between the OPIs and GPIs showed that there are differences in the information that is provided under the various headings that were analysed in the package inserts. The key findings have been summarised below.

The OPI and its corresponding GPI are not consistent in the information that it provides to the health care providers and to patients. Research conducted internationally indicates that this finding is not unique and that there is a lot of variability in the important information across all the investigated markets (Pfistermeister, et al., 2013). The listed contraindications, warnings, interactions, side-effects and precautions are more comprehensively provided for in the GPI. The GPI was able to provide important latest information that was not present in the OPI. The additional information provided in the GPI resulted in a PI that was of improved quality when compared to the OPI. However, if a patient or health care provider had to compare the information provided in the GPI and OPI it would appear different. The removal of clinical and non-clinical information as requested by the health authority evaluators and the additional information presented in the GPI could make it seem that the generic medicine is not as safe because it lists more contraindications and has more warnings, side-effects and special precautions than the OPI. The removal of non-clinical data from the GPI is of concern as the registration of generic medicines is based on the clinical and non-clinical studies that have been carried out using the originator medicine. A generic medicine is manufactured with the intention of being an alternative more cost-effective option for therapy but the differences noted between the OPIs and GPIs makes one question whether it really is equivalent to the originator medicines. This may affect physician and patient confidence with the use of generic medicines.

3.3 Sources of information used to compile a GPI

SAHPRA guidelines do provide a list of reference sources that could be used for the compilation of a GPI. Discussions during the focus group generated additional sources of information that regulatory staff use to compile a GPI. Table 10 shows the reference

sources listed by SAHPRA compared to the list of reference sources provided by the participants of the focus group.

Table 10 Reference sources used for compilation of a GPI – SAHPRA recommended sources vs actual reference sources used

SAHPRA recommended reference sources	Actual reference sources used
• Most recently approved innovator PI • Reference books: - Good & Gilman - Martindale - USP dispensing information • Company core data sheet is only considered if substantiated by relevant data on which it is based • Other references or peer reviewed updated references, including information obtained from other regulatory authorities with which the Council aligns itself • SAHPRA monographs • SAHPRA guidelines[1]	• Most recently approved originator PI available in the local commercial pack • Reference books: - Good & Gilman - Martindale - USP dispensing information • Company core data sheet is only considered if substantiated by relevant data on which it is based • Other references or peer reviewed updated references, including information obtained from other regulatory authorities with which the Council aligns itself • SAHPRA monographs • SAHPRA guidelines • **Most recently approved originator PI available overseas**

[1] SAHPRA guidelines for PIs comprise of the following guidelines:
PIs for Human Medicines, 2014
Labelling of medicines containing sugars, 2015
Patient Information Leaflets, 2014
PIs for Human Medicines Standardised Texts, 2015

	• **Most recently approved PI for the same medicine that is being applied for, that has already received approval by overseas regulatory authorities** • **Latest edition of the Summary of product characteristics (SmPC), mainly the United Kingdom version**

As per the SAHPRA guidelines, pharmaceutical companies are required to use the most recent approved originator PI (PI) as the reference for the compilation of a generic PI. The guidelines state that the indications, dosage and directions for use and the safety profile for a generic medicine should at least be in line with that of the originator PI. The guideline also states that SAHPRA retains the discretion to require more or less details under the respective headings of the PI.

SAHPRA guidelines recommend that applicants use the reference book Goodman & Gilman, to include additional information relating to pharmacological action. The Martindale is used for additional information relating to safety information. Other supplementary reference sources may be used i.e. USP Dispensing information, SAHPRA monographs and peer reviews references.

Carol explained that SAHPRA guidelines are used primarily for structure and layout of the GPI. The guidelines are also useful when standardised texts for a specific condition or class of medicine is required or for when the sugar content of the medicine needs to be included. Other than for the reasons stated above, the OPI that is available in the local commercial pack is the primary reference source that is used to compile the GPI.

Carol emphasized that the approved OPI that is registered overseas and/or the UK Summary of Product Characteristics (SmPC) are used for compilation when the local originator PI is outdated and does not contain the most recent available safety data. The

SmPC is obtained electronically via the electronic medicines compendium (eMC) website and the document contains up to date, approved and regulated prescribing and patient information for licensed medicines. All the participants of the focus group agreed that the information under the headings contraindications, side-effects, warnings and special precautions of the GPI are updated in line with the overseas OPI and/or the UK SmPC.

A significant finding is that the regulatory staff align the GPI to the latest information that is available internationally. The reason for the alignment with international information is because the local OPI is outdated. The company has its own set of global standards which has to ensure that the patient is protected from receiving outdated information, that the company is protected from reputational damage and that there is consistency in the labelling information in all products that are marketed internationally. The company is at a risk of being sued should important information be left out of the GPI.

3.4 Processes followed in the compilation of a GPI

3.4.1 Health authority process

The health authority has not published a process for the compilation of a GPI. Guidelines have been published that provide information on the structure and content of the PI, however, the actual process has not been documented. Further to this there are no timelines allocated to the evaluation process. Once a GPI has been submitted for evaluation, there is no information provided as to when the pharmaceutical company can expect an outcome. Carol said that “it could around 4 years to receive the first clinical committee recommendation”.

3.4.2 Internal process

The focus group discussion revealed that there is agreement among the pharmacists about the process that is followed to compile GPIs. The process can be summarised into eight steps, refer Figure 1. Carol confirmed that the internal process that is described below has been developed by the regulatory staff through experience.

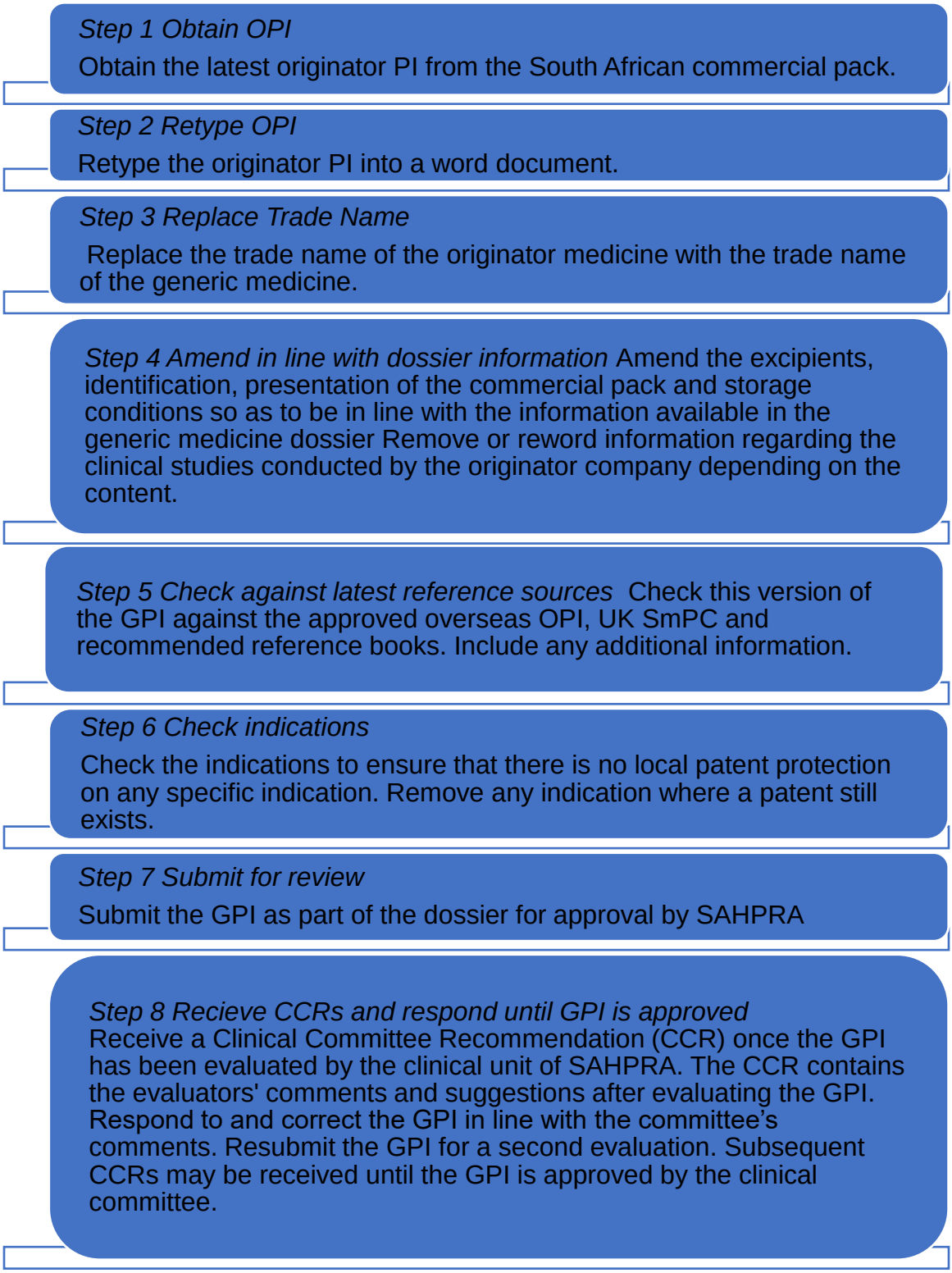


Figure 1 Eight steps of GPI compilation

3.4.3 Amendment process

The PI of registered medicines can only be changed or amended upon approval from SAHPRA. SAHPRA has provided an amendments guideline that allows for amendments to be done on registered medicines, however, there is no guidance on timelines for approval. Carol said that, “it could take around 1 ½ years for the applicant to receive any outcome”.

Bridget commented that “there is no process for regulatory staff to contact SAHPRA to find out if there is an outstanding amendment on a medicine”. This provides a possible explanation as to why the local OPIs that were used in the textual analysis did not contain all the latest safety information that the GPI contained. It is possible the originator company has applied for an amendment to the OPI, however, they have not received any outcome from the health authority and hence are unable to update their PI.

3.5 Experiences and perceptions of regulatory affairs personnel

3.5.1 Accessibility of the local OPI

During the focus group discussion, the participants explained that whilst the most recent local originator PI is the primary reference to be used for the compilation of a generic medicine PI, it is very difficult to obtain the most recent version. Often the PI that is available in the commercial pack of the originator medicine in South Africa is outdated and not in line with the corresponding overseas originator PI or UK SmPC. Bridget said that, “the compiler will include the latest updated information from the overseas originator PI and/or the UK SmPC into the GPI in order to ensure that the generic medicine PI contains the latest information”.

The latest safety information from acceptable reference books will also be included to ensure that the GPI contains the most updated information available at the time. This is often the reason why differences arise in the information presented in the OPI and the GPI. This is also the main reason why the side effect profile, warnings and special

precautions of the generic medicine is more extensive than that of the local originator medicine.

In the European Union (EU) and the United States (US), it is a requirement for originator companies to update their PIs in line with phase IV clinical trial data, pharmacovigilance data and ongoing research (Filby, 2007). It is therefore also possible that an amendment may have been submitted by the originator company, to SAHPRA to update the information that is available in the local OPI available in the commercial pack. Miya said that, “due to long timelines for review by SAHPRA the amendment may not be reviewed for many years and hence the originator medicine PI available in South Africa will not be in line with the latest information that is available globally”. The generic pharmaceutical company will also not have oversight of the pending amendment on the OPI as there is no system in place to gain access to this information.

3.5.2 Administrative issues

One of the issues that emerged from the focus group was the room for error in the procedure because the local OPI is retyped into a word document. Thea said that, “there is a possibility for errors to be made and for information to be missed out or repeated”. Thea and Lynn said that, “due to time constraints, the word document may not be peer reviewed and hence the error will be submitted in the final version of the GPI”. SAHPRA evaluators may not pick up this error during evaluation and this will lead to the information that is present in the OPI being different to that presented in the GPI.

Thea, Bridget and Tammy said that, “they experience a lot of frustration in retyping an OPI into a word version for editing”. Longer complex medicine PI e.g. antiretroviral medicines (a combination of multiple active ingredients) PIs are at greater risk due to the amount of information that needs to be retyped. Thea described the process as time consuming and exhausting.

3.5.3 Patent issues

Another issue that was raised by Carol was around patent issues which SAHPRA does not concern itself with. Bridget said that, “it is the responsibility of the company to ensure that the patent issues are checked prior to product launch”. Currently regulatory staff at the company remove indications due to an existing patent. This is a patent protection strategy that originator companies use to ensure market exclusivity. Hence the approved GPI may not contain some of the indications present in the OPI due to patent protection. Due to the long timelines for review, the regulatory staff find that once the GPI is approved, the patent on the indication has already expired and an application to include the indication on the GPI then needs to be submitted to SAHPRA for approval. This means that the product would be launched without the indication being listed on the GPI and only once approval has been obtained from SAHPRA can the indication be added into the GPI.

Carol explained that as per the company’s global policy all indications should be applied for at once and then prior to launch the applicant should remove those indications that have patents and only include them onto the PI once the patent has expired. The process of removing patented indications is internally referred to as “Carving”. If SAHPRA were to implement this system it would prevent another application having to be submitted in order to add a new indication. This would lead to a decreased workload on the side of the health authority and on the regulatory staff of the company. It would also allow for the generic medicine to be used for an additional indication as soon as patent expiry without having to wait for approval from the health authority.

3.5.4 Challenges in dealing with the health authority

All the regulatory staff described the process of compiling and submitting a GPI for approval by SAHPRA as frustrating and inconsistent. Lynn felt strongly that the system lacks transparency, reproducibility and overall integrity.

3.5.4.1 Quality of the Clinical Committee Recommendation (CCR)

The group noted that clinical committee recommendations received from the evaluators are often inconsistent. Bridget, Tammy and Thea said that, “the information that has been requested for inclusion in the first CCR received from evaluators is asked to be removed in the second CCR”. There is no reason or justification given for the removal. This leads to a lot of frustration as the staff member compiling the PI does not know why the evaluator is requesting the removal. Lynn said that, “a possible reason for this is that the PI is not reviewed by the same evaluator each time and hence each evaluator will have a different opinion on whether the information should be present or not”. The level of training and skill set of the evaluators are not known. The applicant has to comply with the recommendations of the evaluators or face a further delay in approval. Lynn said that, “the allocation of a specific product to a specific team of evaluators rather than to any available evaluator would reduce the number of inconsistencies received in CCR”.

Carol said that, “It very unusual for a product to only receive one clinical recommendation”. The product will most likely receive a second or third recommendation for information to be included or excluded or amended. This contributes to a very long delay in the approval of a GPI. Most times the second or third recommendations focus on spelling or the inclusion of a comma or a full stop. The focus of the evaluation shifts from actual medical content to finding spelling and grammar errors. All the participants of the focus group agreed that delaying a product’s approval because of a full stop, comma or spelling mistake is extremely frustrating as the applicant could wait a further 3 – 6 months in order to gain clinical approval.

Tammy said that, “at times, clinical committee recommendations request the applicant to justify statements that were taken directly from the OPI. It is possible that the OPI may not have been updated to the latest information available but the information was included since it is presented in the commercially available OPI.

Thea explained that there are situations were recommendations received from the pharmaceutical and analytical unit mimic that received from the clinical unit. This results in a duplication of work. Communication between the different units of the health authority would prevent this from occurring and would also save time and resource for the health authority and the applicant.

Lynn said that, “the GPIs are also manually assessed and the evaluators comments are written in pen on a hard copy of the GPI”. The annotated GPI is then sent to the applicant. At times, staff members are unable to decipher what has been written on the GPI or what needs to be corrected. The comments are vague and the staff member compiling the response is left to interpret what he or she thinks is correct and respond accordingly. Should the regulatory staff misinterpret what is required then an additional CCR would follow leading to a further delay in approval.

3.5.4.2 Communication and transparency

Carol said that, “there is no opportunity for a regulatory staff member to contact or approach the evaluator”. The staff members explained that when they try to call or email SAHPRA they are often unsuccessful. If somebody does answer the phone, they are at most times unable to assist or hesitant to assist. Lynn said that, “it is not possible to know the names of the evaluators or to speak or contact them directly. The process is not transparent and it is difficult to follow up on the approval of products or even to determine product status”.

Foreign regulatory authorities employ the use of more transparent review systems. As discussed in the literature review, both the TGA and the EMA provide public assessment reports upon review completion. The timelines for assessment by the EMA are clearly defined. Applicants are allowed to contact the evaluator during the approval process. A meeting or telephone call is arranged to discuss any queries.

The above issues ultimately highlight the impact that the evaluator has on the overall approval process. Lynn said that, “if evaluators were accessible this would allow applicants to contact them directly and set up meetings or telephone calls to discuss

questions raised by the applicant". This would favour approval timelines instead of receiving numerous CCRs and would also lead to decreased work load for the applicant and the health authority.

Tammy and Bridget said, "that there have been cases where the responses to clinical recommendations have been mislaid". They had received no communication from the health authority that the response has been mislaid. This was discovered when they had contacted the health authority via telephone in order to obtain a product status. No subsequent written communication was received. Thea and Bridget had to resubmit the response and this contributed to a further delay in obtaining approval. The health authority did not fast track this response and it waited in the queue for assessment.

3.5.4.3 Amendments

Lynn said that, "the amendments of currently approved PIs also take a very long time for approval". Companies may need to do multiple updates to PIs and find themselves in a situation where the last amendment was not as yet approved and they already have to submit a new amendment. This causes a lot of confusion and results in the GPI that is present in the commercial pack being outdated and not in line with the foreign GPI available in overseas countries for the same product. This poses a risk as patients in South Africa do not have access to latest available medicine information.

3.5.4.4 Clinical committee meeting dates

Currently clinical committee meetings are held at set dates that are determined by the health authority. This results in outcomes for multiple products being received at the same time. Lynn said that, "it would be useful if products could be discussed sooner rather than waiting for a clinical meeting date". This would allow applicants to receive recommendations as soon as they become available from evaluators. This would ultimately shorten the timelines for approval. Carol said that, "the current system needs to be revised".

3.5.4.5 Health authority backlog

The health authority has acknowledged that a backlog exists and that the evaluation of products have been delayed. This is attributed to a lack of skilled staff and also due to a lack of service level agreements between the external evaluators reviewing the PIs and the health authority. Lynn said that, “the lack of proper evaluation and review systems coupled with human resource challenges contribute to the current backlog and hence the review process takes a long time to complete”.

3.6 Summary of the focus group discussions (Second Data Set)

The focus group discussion was conducted with regulatory affairs personnel who identified the sources of information that are used to compile the GPI. SAHPRA have recommended a list of sources that must be used to compile a GPI, however, the regulatory affairs personnel use additional sources of information to compile the GPI. The inclusion of additional information from additional sources results in a difference in the information that is provided in the GPI. The information that is included into the GPI is in line with the latest overseas OPI and/or the UK SmPC. The regulatory staff have had to use these additional resources for information as the primary source as recommended by SAHPRA, the local OPI, is considered outdated due to the omission of the latest product information available in the overseas OPI and UK SmPC. These findings are noted in the OPI for Atacand® in which the date of PI publication is listed as 30 November 2007. This date indicates that the OPI was last updated approximately 10 years ago.

The regulatory affairs personnel identified the process that was used for the compilation of a GPI. The process used was described in eight steps. Currently SAHPRA have not recommended a process for the compilation of a GPI. The regulatory personnel have formulated these steps through their years of experience in compiling GPIs. Since SAHPRA have not recommended a process, the staff had to formulate their own process in order to ensure consistency of GPI compilations within the pharmaceutical company. The timeline for evaluation of a GPI and subsequent receipt of a clinical

committee recommendation by the applicant is unknown. The process of amending a PI that has already gained SAHPRA approval is challenging and there are no clear timelines on how long this process can take. This could be a reason that explains why the local OPIs have been not been updated.

The experiences and perceptions of the regulatory affairs personnel in compiling a GPI for approval by SAHPRA was explored. The regulatory staff have had many challenges in compiling the GPI, including accessibility to the latest local OPI. Due to the local OPI being outdated staff had to seek other sources of information to ensure that the GPI contained the most up to date information that is available globally. The staff also faced administrative issues. Manual typing up of the local OPI creates room for errors in the GPI. Applications to include additional indications into an approved GPI took long and resulted in an additional workload for both the applicant and the health authority.

Another enormous challenge for the regulatory staff was the communication with the health authority. A GPI must undergo evaluation by the evaluators of the health authority prior to approval. The evaluators assess the GPI and determine which information should be deleted, added or amended. The review process is a contributor to the differences that were noted in the textual comparisons. The regulatory staff experience very poor levels of communication with the health authority. They are unable to contact the evaluators and even experience challenges in obtaining a product status via phone or email. There is no online system available to track or view the progress of a GPI that has been submitted for approval. The system lacks traceability and transparency.

CHAPTER 4 CONCLUSIONS AND RECOMMENDATIONS

The study evaluated the differences noted between the information presented in the originator medicine PI and the generic medicine PI. This comparative analysis of the PIs was manually performed using checklists. A focus group discussion was conducted with regulatory staff participants, involved in the compilation of generic medicine PIs, from one pharmaceutical company. The participants are involved in the compilation of generic medicine PIs. The differences noted in the textual analysis was discussed in the focus group. The sources of information that are used and the regulatory process that is followed for the compilation of a generic medicine PI was identified. The study explored the experiences and perceptions of the regulatory staff with regard to compiling a generic medicine PI for approval by the South African Health Product Authority.

4.1 Summary of findings

As mandated by SAHPRA, the contents of a generic medicine PI (GPI) should be the same as that presented in the originator medicine PI because its compilation is based on the information present in the OPI. The results of the comparative textual analysis showed that this is not the case. The analysis showed that there was a large number of differences between the information presented in generic and originator medicine PIs. The GPI contained additional information under the various headings of the PI i.e. Contraindications, warnings, interactions, side-effects and special precautions. The additional information presented in the GPI was included by regulatory pharmacists who were responsible for the compilation of the GPI. The information was obtained from the latest information that was available in the list of reference sources used by the regulatory affairs staff (refer Table 10). The information that was included into the GPI was important to both the health care provider and the patient.

The inclusion of additional latest information into the GPI resulted in it being a more comprehensive and accurate source of information than the OPI. Although the GPI was shown to contain vital information that the OPI lacked, it does eventually result in different information being provided in PI sources that are expected to be the same. The

exclusion of clinical and non-clinical data accompanied with the comprehensive side-effect profile, additional contraindications, warnings, interactions and special precautions may lead one to believe that the generic medicine is not the same as the originator medicine even though the molecule contained in originator and the registered generic medicine is the same. It could also be perceived that the generic medicine is less safe because it has more side effects and more contraindications, warnings, interactions and special precautions. Patients may also believe that this is the reason why generic medicine is available at a cheaper price. It is therefore ironic that the increased quality of the GPI may undermine patient confidence when deciding to use generic medicines.

The study found that the differences noted in the OPI and GPI could be attributed to the sources of information used to compile the GPI and the health authority review process. SAHPRA recommended that the latest locally available OPI be used as the primary source for compilation of the GPI, however, this is not what happens in practise. The local OPI is outdated and regulatory staff are then forced to seek alternative sources of information to ensure that the GPI contains the latest information that is available. Generic companies have to adhere to their own set of internal global standards and also need to ensure that they are not sued by patients should the information in the GPI be incorrect or inadequate. SAHPRA have not recommended a process for the compilation of a GPI or the amendment of an already registered GPI. Regulatory pharmacists draw on their regulatory experiences and decide on the best way of GPI compilation.

The local health authority process is flawed and does not support the timeous registration and access to generic medicine. There are no confirmed timelines for the approval of a generic medicine PI or an amendment to an already registered GPI. The regulatory process for compilation and approval of a GPI is unclear. The manual assessment of the GPIs by the health authority evaluators as well as a lack in the standardisation of recommendations received results in many reviews of the GPI prior to approval being obtained. The lack of an electronic tracking tool makes it difficult to track and trace the status of a GPI. Communication channels with the staff of the health authority are limited and the interaction is often very poor. The lack of timelines and a

structured, transparent system for generic medicine review contributes to a delay in registration and ultimately a delay in access to generic medicine.

4.2 Recommendations

The regulatory staff at the pharmaceutical company describe the process of compilation and approval of a GPI as inconsistent and frustrating. The following recommendations are proposed:

- The current SAHPRA system lacks transparency. Applicants are unable to trace the submission of documents or find out the status of their applications in the system. The development of an electronic tracking tool will allow applications to be efficiently traced. Applicants would be able to log into the system using a user specific password and information relating to the application can then viewed. This system will also prevent the numerous follow up emails and telephone calls that are made to the health authority in out to determine product status.
- One of the reasons that regulatory pharmacists seek other sources of information for compilation of the GPI is because the local OPI is outdated. The creation of an electronic access portal that contains the currently registered local and overseas OPIs and GPIs for all molecules, as well as the status of any pending amendments would allow applicants to view the status of already registered OPIs and GPIs. This would assist applicants in determining whether there is a pending amendment on the current OPI that was obtained in the commercial pack. Applicants may then refer to the pending amendment in the submission of the GPI. The portal should allow the public to gain access to the latest available PI for any product.
- The current SAHPRA system does not enforce any system for the updating of already approved PIs. This leaves the decision up to applicants who may choose not to update their PIs and hence the PI in the commercial pack may become outdated. The implementation of a mandatory updating system for all approved PIs will ensure that the commercial pack contains the latest approved PI.
- The regulatory staff stated that the communication channels between the applicant and SAHPRA are very poor. The improvement of communication channels would enhance

the relationship between the applicant and the health authority. SAHPRA could consider using communication tools such as email and telephone calls to facilitate communication with the applicant.

- The current guidelines issued by SAHPRA for PI compilation lacks standardization and creates room for applicants to submit the GPI in different ways. The development of guidelines for the compilation of a GPI would assist pharmaceutical companies in standardising the applications that are submitted for review. This will assist evaluators as the quality of submissions will be improved through standardization. This could potentially aid in quicker review and approval timelines.
- The current SAHPRA system lacks transparency and openness. The implementation of public assessment reports would allow applicants to view the reasons for approval or rejection of an application. The inclusion of the name and contact details of the reviewer would allow applicants to be able to contact the reviewer in the event of a query. This would prevent the GPI from having to undergo multiple reviews and ultimately results in a decreased workload for both the health authority and the applicant. This could potentially lead to quicker review and approval timelines.
- The quality of the Clinical Committee Recommendations (CCRs) received from the health authority have been reported as poor. The provision of training to health authority evaluators and applicants by the health authority would improve the quality of CCRs and also standardise the clinical committee recommendations and applicant responses to the recommendations. This could aid applicants in understanding the requirements of the evaluators and ensure that the responses adequately meet these requirements.
- SAHPRA have confirmed that there is a lack of skilled resources. Head hunting and the employment of additional experienced staff members with agreed service level agreements will contribute to the efficient and timeous review of GPIs.
- The current SAHPRA system does not function optimally and at times submissions made by applicants are lost. The applicant may become of the lost documentation through follow up with the health authority. A fast track system should be considered for applications that were mislaid to ensure that these applications are not further delayed.
- There are no specific timelines for the review and approval of a GPI in South Africa. Benchmarking against foreign regulatory authorities that have specific review timelines

and transparent review systems would ultimately result in the overall improvement of the current system. The EMA have stipulated timelines allocated to each stage of the medicine approval process (Kashyap, Gupta, & Ragunandanh, 2013). Figure 2 shows the allocation of timelines for the decentralised procedure used by the EMA. The use of a similar model in South Africa would be advantageous.

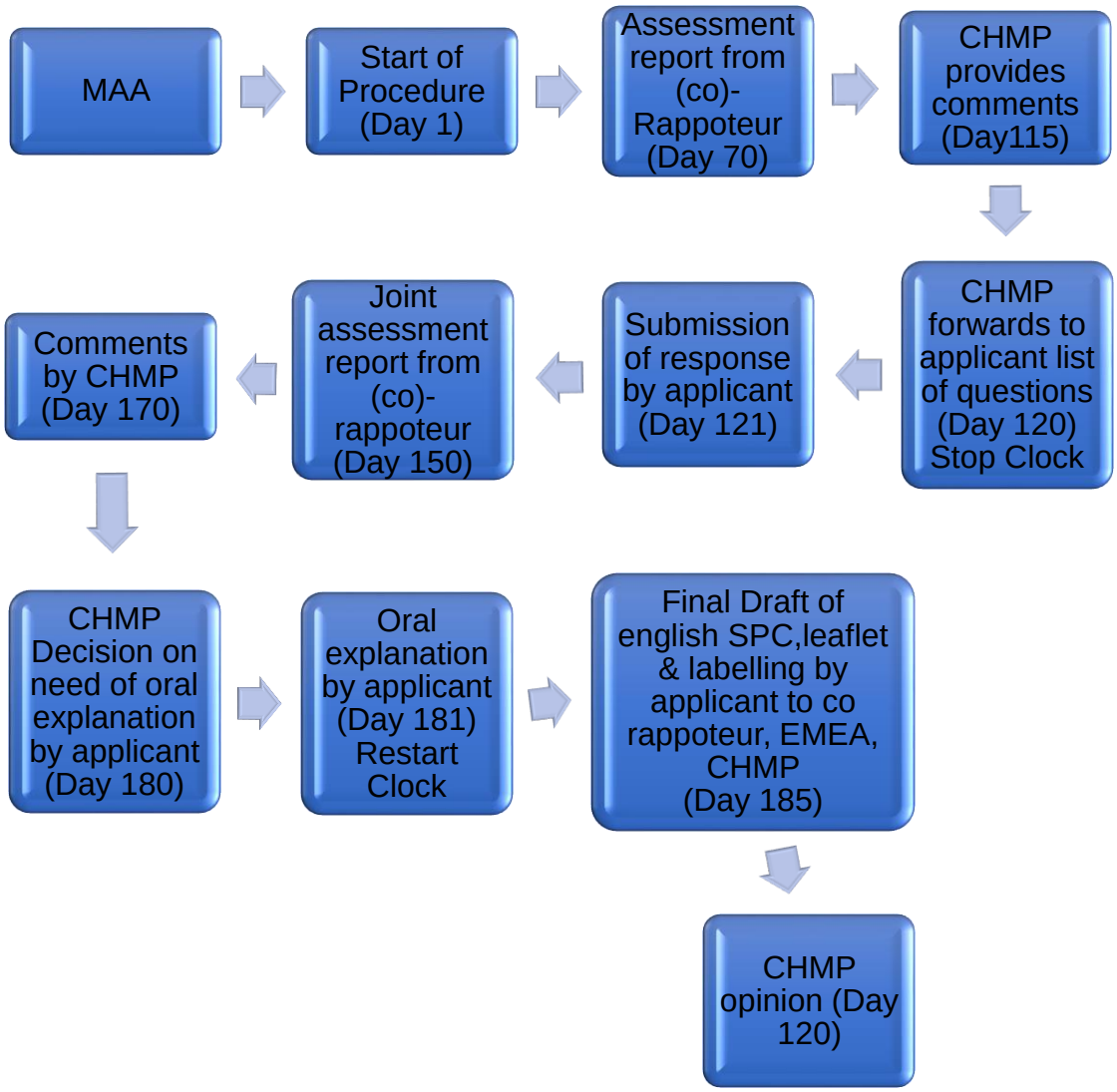


Figure 2 Decentralised process with timelines

- The current SAHPRA system has no notification system. Applicants do not know if the GPI was successfully received, if the application is under review or if the GPI has been approved. The use of email notifications to applicants would allow applicants to immediately know the status of a GPI and they would to be able to communicate the product status to the greater business. Knowing the status of products in the system allows applicants to be able to efficiently plan their commercial strategies. This becomes very important with the launch of first to market generics where timing becomes crucial. This would encourage a sense of accountability of the part of the health authority. Figure 3 proposes stages at which the health authority should send out notifications to the applicant.



Figure 1 Proposed stages of email notifications

- The regulatory pharmacists have expressed that mistakes can happen through manual typing of the GPI. Generic pharmaceutical companies should consider employing administrative staff to type up word versions of the OPI, or invest in electronic tools that could carry out this process. The word version must be checked for accuracy prior to being used for compilation of the GPI. This would eliminate the potential for errors in the text.

The above recommendations would improve the transparency of the process and would facilitate the timeous review of generic medicine PIs. The mandatory updating of approved PIs would allow for the alignment of information presented in the GPI and OPI. The local health authority is in a period of transition. The change from MCC to SAHPRA creates an opportunity for the implementation of amendments to current guidelines and systems.

There are no current timelines for the review and approval of a GPI. This results in GPIs being evaluated many years after their initial submission. A generic medicine can only be approved by SAHPRA once all the areas of safety, quality and efficacy have been adequately addressed. The GPI is one of the components of registration that must be approved before the registration of a medicine. Since this process is currently taking so long, access to generic medicines is being delayed. The recommendations of this study suggest ways in which the review and approval process can be improved and essentially accelerated. Many patients and health care providers may be hesitant to use generic medicine however this study shows that in many instances the GPI contained the latest safety information that was not present in the OPI. The results of this study provide data that show that this is the case. This information could therefore potentially assist in improving the access and acceptance of generic medicines.

This study focused on a single pharmaceutical company. Further research conducted on GPIs registered and the regulatory processes followed by other pharmaceutical companies would be useful in determining if the results are consistent with the findings of this research. Similar research using a larger sample size in other therapeutic classes of medicines would also be useful in determining the consistency of the research findings.

It would also be interesting to conduct an analysis of PIs of the same products utilised in this study but sourced from different countries to establish if comparable findings are obtained.

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APPENDICES

Appendix A: Assessment of Drug Information

Table 1: Assessing drug information for candesartan cilexetil.
A comparison between ATACAND® 8 mg, 16 mg, 32 mg (Originator brand) and GENERIC CANDESARTAN 8 mg and 16 mg (Generic medicine)

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Indications	**Yes**	**No**	
Mild to moderate hypertension	✓		
Can be used as monotherapy or in combination with other antihypertensive agents such as thiazide diuretics and dihydropyridine calcium antagonists, for enhanced efficacy	✓		
Heart failure: treatment with ATACAND reduces mortality, reduces hospitalization due to heart failure, and improves symptoms in patients with left ventricular systolic dysfunction (LVEF ≤ 40%)	✓		
Total Statements: 3	**3**	**0**	**0**
Contraindications			
Hypersensitivity to any component	✓		
Very severely impaired renal function (creatinine clearance < 15 ml/min)		✓	**Different statement:** (creatinine clearance < 30 ml/min)
Pregnancy and lactation	✓		
Severely impaired hepatic function		✓	
Bilateral renal artery stenosis or stenosis in the presence of a single kidney	✓		
Aortic valve stenosis or Hypertrophic Obstructive Cardiomyopathy (HOCM)	✓		
Angioedema on previous exposure to ATACAND or angiotensin receptor blockers (ARB's) or ACE inhibitors	✓		

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Contraindications	**Yes**	**No**	
			Additional statement: **Hereditary or idiopathic angioedema**
			Renal artery stenosis in patients with a single kidney
			Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride
			Porphyria
			Lithium therapy: Concomitant administration may lead to toxic blood concentrations of lithium
Total Statements: 7	**6**	**1**	**5**
Warnings			
When ATACAND is used in patients with severe renal impairment, period monitoring of serum potassium and creatinine levels should be considered. There is very limited experience in patients with very severe or end stage renal impairment (creatinine clearance < 15 ml/min/1,73 m^2 BSA)		✓	**Different statement:** **(creatinine clearance < 30 ml/min/1,73 m^2 BSA**
Refer to pregnancy and lactation for warnings	✓		**Additional Statement:** **Should a woman become pregnant while receiving GENERIC CANDESARTAN, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine**
Total Statements: 2	**1**	**1**	**2**

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
No interactions of clinical significance have been identified	✓		
Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives, glibenclamide, nifedipine and enalapril		✓	**Deleted statement and different statement:** Warfarin and enalapril have been excluded however information specific to warfarin has been mentioned as an additional statement below
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with ATACAND and careful monitoring of serum lithium levels is recommended during concomitant use.	✓		
The antihypertensive effect of ATACAND may be enhanced by other antihypertensives.	✓		
The bioavailability of candesartan is not affected by food.	✓		
			Additional statement: Post marketing reports suggest a rare but significant interaction with increase of INR and bleeding with concomitant warfarin therapy
Total Statements: 5	**4**	**1**	**2**
Dosage and Directions for use			
Recommend initial dosage 8 mg once daily	✓		
Usual maintenance dose is 8 mg to 16 mg once daily	✓		
The maximal antihypertensive effective is attained within 4 weeks of initiation of treatment	✓		
Some patients may receive an additional benefit by increasing the dose to 32 mg once daily	✓		

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Dosage and Directions for use	**Yes**	**No**	
Use in elderly: No initial dose adjustment necessary for patients with normal renal & hepatic function	✓		
Use in impaired renal function: No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 ml/min/1.73 m^2 BSA). In patients with more severe renal impairment (i.e. creatinine clearance < 15 – 30 ml/min/1.73 m^2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be used.		✓	**<u>Different statement in patients with more severe renal impairment:</u>** **In patients with more severe renal impairment (i.e. creatinine clearance < 30 ml/min/1.73 m^2 BSA), GENERIC CANDESARTAN is contraindicated**
Use in impaired hepatic function: No initial dosage adjustments is necessary in patients with mild to moderate hepatic impairment. There is no experience available in patients with severe hepatic impairment and/or cholestasis	✓		**<u>Additional statement:</u>** **A lower initial dose of 4 mg should be considered**
Concomitant therapy: ATACAND can be used as monotherapy or in combination with other antihypertensive agents such as thiazide diuretics and dihydropyridine calcium antagonists e.g. amlodipine, for enhanced efficacy	✓		
Use in black patients: Antihypertensive effect of ATACAND is less in black than non-black patients. Consequently, up titration of ATACAND and concomitant therapy (such as thiazide diuretics) may be more frequently needed for blood pressure control in black than non-black patients	✓		
Dosage in heart failure: The usual recommended initial dose is 4mg once daily. Up-titration to the target dose of 32 mg once daily or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks	✓		

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Dosage and Directions for use	**Yes**	**No**	
Special patient populations: No initial dose adjustment is necessary for elderly patients or in patients with renal or mild to moderate hepatic impairment	✓		
Concomitant therapy: ATACAND can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitals or a combination of these medicinal products	✓		
Administration: once daily with or without food	✓		
Use in children: Safety and efficacy have not been established in children	✓		
Total Statements: 14	**13**	**1**	**2**
Side Effects			
The overall incidence of adverse events showed no association with dose, age or gender		✓	
In a pooled analysis of clinical trial data, the following common adverse reactions with candesartan cilexitil were reported based on an incidence of adverse events with candesartan cilexitil at least 1 % higher than the incidence seen with placebo		✓	
Infections and infestations: Common: Respiratory infection	✓		
Nervous system disorders: Common: Dizziness/vertigo, headache	✓		
Laboratory findings: Small decreases in haemoglobin have been seen. Significant increases in creatinine, urea or potassium and decrease in sodium have been observed. In patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered	✓		**<u>Part of the statement is deleted:</u>** **Significant increases in creatinine, urea or potassium and decrease in sodium have been observed.**

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
Treatment of heart failure: The adverse experience profile of ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM clinical programme, comparing ATACAND in doses up to 32 mg (n = 3803) to placebo (n = 3796), 21.0 % of the candesartan cilexitil group and 16,1 % of the placebo group discontinued treatment because of adverse events.	✓		**<u>Part of the statement is deleted:</u>** **In the CHARM clinical programme, comparing ATACAND in doses up to 32 mg (n = 3803) to placebo (n = 3796), 21.0 % of the candesartan cilexitil group and 16,1 % of the placebo group discontinued treatment because of adverse events.** **<u>Additional statement:</u>** **The most frequently reported adverse reactions were hyperkalaemia, hypotension and renal impairment. These events were more frequent in patients over 70 years of age, diabetics or subjects who received other medicinal products**
Vascular disorders: Hypotension	✓		
Metabolism and nutrition disorders: Hyperkalaemia, hyponatraemia	✓		
Renal and urinary disorders: Renal impairment including renal failure in susceptible patients	✓		
Blood and lymphatic system disorders: Leucopenia, neutropenia and agranulocytosis	✓		
Hepato-biliary disorders: Increased liver enzymes, abnormal hepatic function or hepatitis	✓		
Skin and subcutaneous tissue disorders: Angio-oedema, rash, uticaria, pruritis	✓		**<u>Part of the statement is deleted:</u>** **Angio-oedema is excluded on GPI and stated on its own under immune system disorders**
Musculosketal, connective tissue and bone disorders: Back pain	✓		**<u>Additional statement:</u> Less frequent: Arthralgia and myalgia**

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
			<u>Additional statements:</u> **Immune system disorders:** **Less frequent: Angioedema** **Gastrointestinal disorders:** **Less frequent: Nausea**
Total Statements: 13	**11**	**2**	**7**
Special precautions			
Hypotension: May occur during treatment with ATACAND in heart failure patients. As described for other agents acting on the renin-angiotensin-aldosterone system, it may also occur in hypertensive patients with intravascular volume depletion. Caution should be observed when initiating therapy and correction of hypovolaemia should be attempted	✓		
Renal artery stenosis: Medicines that affect the renin-angiotensin-aldosterone system may increase blood urea & serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney	✓		

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Renal impairment: As with other agents inhibiting the renin-angiotensin-aldosterone, changes in renal function may be anticipated is susceptible patients treated with ATACAND. When ATACAND is used in hypertensive patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered. There is very limited experience in patients with very severe or end stage renal impairment (i.e. creatinine clearance < 15 ml/min/1,73 m^2 BSA). Evaluation of patients with heart failure should include periodic assessments of renal function. During dose titration of ATACAND, monitoring of serum creatinine and potassium is recommended.	✓		**Part of the statement is deleted:** **When ATACAND is used in hypertensive patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered. There is very limited experience in patients with very severe or end stage renal impairment (i.e. creatinine clearance < 15 ml/min/1,73 m^2 BSA).**
Kidney transplantation: There is no experience regarding the administration of ATACAND in patients with recent kidney transplantation	✓		
Hepatic impairment: There is no experience in patients with severe hepatic impairment and/or cholestasis	✓		
Aortic and mitral valve stenosis: Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy		✓	**Different statement:** **GENERIC CANDESARTAN is contraindicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy**

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Hyperkalaemia: Concomitant use of ATACAND with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that may increase serum potassium levels may lead to increases in serum potassium in hypertensive patients. In heart failure patients treated with ATACAND, hyperkalaemia may occur. During treatment with ATACAND in patients with heart failure, periodic monitoring of serum potassium is recommended, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone	✓		
Anaesthesia & surgery: Hypotension may occur during anaesthesia and surgery in patients treated with ATACAND due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors	✓		
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.	✓		

ATACAND®	GENERIC CANDESARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
General: In patients, whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterine system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicines that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. Excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.	✓		
Effects on ability to drive and use machines: The effect of ATACAND on the ability to drive and use machines has not been studied. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment	✓		
Total Statements: 11	**10**	**1**	**2**

Table 2: Assessing drug information for telmisartan.

A comparison between MICARDIS® 40 mg and 80 mg (Originator brand) and GENERIC TELMISARTAN 40 mg and 80 mg (Generic medicine)

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Indications	**Yes**	**No**	
Treatment of mild to moderate hypertension, either alone or in combination with hydrochlorothiazide	✓		
Total Statements: 1	**1**	**0**	**0**
Contraindications			
Hypersensitivity to any of the components	✓		
Severe hepatic impairment	✓		
Severe renal impairment	✓		**Additional statement:** Creatinine clearance, 30 ml/min
Biliary obstructive disorders	✓		

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Contraindications	**Yes**	**No**	
			<u>Additional statements:</u> **A history of angioedema related to previous therapy with Ace inhibitors or angiotensin receptor blockers (ARB's). Such patients must never be given these medicines.**
			Hereditary or idiopathic angioedema
			Hypertrophic obstructive cardiomyopathy (HOCM)
			Bilateral renal artery stenosis
			Renal artery stenosis in patients with a single kidney
			Aortic stenosis
			Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride
			Porphyria
			Lithium therapy: Concomitant therapy with GENERIC TELMISARTAN may lead to toxic blood levels of lithium
			Pregnancy and lactation
Total Statements: 4	**4**	**0**	**11**
Warnings			
Should a woman become pregnant while receiving MICARDIS, the treatment should be stopped promptly and an alternate medicine used. Should a woman contemplate pregnancy, the doctor should consider alternative medication	✓		
Total Statements: 1	**1**	**0**	**0**

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
May increase the hypotensive effect of other antihypertensive agents	✓		
Compounds which have been studied in pharmacokinetic trials include digoxin, warfarin, HCTZ, glibenclamide, paracetamol, ibuprofen, simvastatin and amlodipine		✓	
For digoxin a 20 % increase in median plasma digoxin trough concentration has been observed (in a single case a 39 %), monitoring of plasma digoxin levels should be considered	✓		
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with MICARDIS. Careful monitoring of serum lithium levels is recommended during concomitant use	✓		**<u>Additional statement:</u>** **Concomitant treatment with NSAIDS (including aspirin at anti-inflammatory dosage regimens. COX-2 inhibitors and non-selective NSAIDS) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin-angiotensin-system, like GENERIC TELMISARTAN, may have synergistic effects. Patients receiving NSAIDs and GENERIC TELMISARTAN should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. A reduced effect of antihypertensive medicines, like GENERIC TELMISARTAN, by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDS**
Total Statements: 4	**3**	**1**	**1**

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Dosage and Directions for use	**Yes**	**No**	
Recommended dose is 40 mg once daily	✓		
Some patients may already benefit at a daily dose of 20 mg		✓	
In cases where the target blood pressure is not achieved the MICARDIS dose can be increased to a max of 80 mg once daily	✓		
Alternatively, MICARDIS may be used in combination with a low dose thiazide diuretic such as hydrochlorothiazide 12,5 mg, which has been shown to have an additive blood pressure lowering effect with MICARDIS	✓		
When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment	✓		
Renal impairment: No dosage adjustment for mild to moderate Hypertension. MICARDIS is not removed from the body by hemofiltration	✓		**Statement is deleted:** MICARDIS is not removed from the body by hemofiltration
Hepatic impairment: In patients with mild to moderate hepatic impairment the dosage should not exceed 40 mg once daily	✓		
Elderly: No dosage adjustment	✓		
Children and adolescents up to 18 years: There is no data on the safety and efficacy of MICARDIS in children and adolescents up to 18 years	✓		
Total Statements: 9	**8**	**1**	**1**

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
The overall incidence of adverse events reported with MICARDIS (41,4 %) was usually comparable to placebo (43,9 %) in placebo controlled trials. The incidence of adverse events was not dose related and showed no correlation with gender, age or race of the patients. The adverse drug reactions listed below have been accumulated from all clinical trials including 5 788 hypertensive patients treated with MICARDIS. The following frequency classification is used: Very common >1/10, common >1/100 and 1/10; uncommon >1/1 000 and < 1/100; rare >1/10 000 and < 1/1000; very rare < 1/10 000		✓	
Infections and infestations: Common: Urinary tract infections (UTI), upper respiratory tract infections.	✓		**<u>Different statement:</u> UTI including cystitis, upper respiratory tract infection including pharyngitis and sinusitis <u>Additional statement:</u> - Sepsis including fatal outcome**
Blood and the lymphatic systemic disorders: Rare: eosinophilia, thrombocytopenia	✓		**<u>Additional statement:</u> Less frequent: Anaemia and neutropenia**
Psychiatric disorders: Uncommon: anxiety Rare: depression, insomnia	✓		
Nervous system disorders: Rare: faintness	✓		**<u>Additional statement:</u> Somnolence, headache, dizziness, fatigue**
Eye disorders Uncommon: abnormal vision	✓		

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
Ear and labyrinth disorders: **Uncommon: vertigo**	✓		
Cardiac disorders: **Rare: bradycardia, tachycardia**	✓		
Vascular disorders **Rare: hypotension**	✓		**Additional statement: orthostatic hypotension**
Respiratory, thoracic and mediastinal disorders: **Rare: dyspnoea**	✓		**Additional statement:** **cough, interstitial lung disease**
Gastro-intestinal disorders: **Common: abdominal pain, diarrhoea, dyspepsia, stomach upset, nausea, vomiting** **Uncommon: dry mouth, flatulence**	✓		
Skin and subcutaneous tissue disorders: **Common: eczema** **Uncommon: increased sweating** **Rare: erythema, pruritis, angio-oedema, urticaria**	✓		**Additional statement:** **drug eruption, toxic skin eruption, rash**
Musculoskeletal, connective tissue and bone disorders: **Common: arthralgia, myalgia, back pain, cramps in legs or leg pain** **Uncommon: tendinitis like symptoms** **Rare: weakness**	✓		**Statement is deleted:** **Weakness is deleted here and listed under general disorders and administration site conditions**
General disorders and administration site conditions: **Common: chest pain, influenza-like symptoms** **Rare: lack of efficacy**	✓		**Additional statement: weakness**

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
Investigations: Infrequently a decrease in haemoglobin or an increase in uric acid have been observed more often during treatment with MICARDIS than with placebo. Increases in creatinine or liver enzymes have been observed during treatment with MICARDIS but these changes in laboratory findings occurred with a frequency similar to or lower than placebo	✓		**<u>Statement is deleted:</u>** **but these changes in laboratory findings occurred with a frequency similar to or lower than placebo**

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
			<u>Additional statements:</u> **Immune system disorders: Less frequent: Anaphylactic reaction, hypersensitivity, angioedema**
			Hepato-biliary disorders: **Less frequent: Abnormal hepatic function/liver disorder**
			Renal and urinary disorders: **Less frequent: Renal impairment, including acute renal failure**
			Description of selected adverse reactions: **Sepsis: An increased incidence of sepsis has been reported with telmisartan compared with placebo**
			Hypotension
			Abnormal hepatic function/ liver disorder: **Most cases of abdominal hepatic function/ liver disorder occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions**
			Interstitial lung disease: Cases of interstitial lung disease have been reported in temporal association with the intake of GENERIC TELMISARTAN
Total Statements: 15	**14**	**1**	**17**

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Renovascular hypertension: There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system	✓		
Renal impairment and kidney transplant: When MICARDIS is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine levels is recommended. There is no experience regarding the administration of MICARDIS in patients with a recent kidney transplant	✓		
Intravascular volume depletion: Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhea or vomiting. Such conditions should be corrected before the administration of MICARDIS. Volume and or sodium depletion should be corrected prior to administration of MICARDIS	✓		
Other conditions with stimulation of the renin-angiotensin aldosterone system: In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria or rarely acute renal failure	✓		

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Primary aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of MICARDIS is not recommended.	✓		
Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.		✓	**Different statement:** **GENERIC TELMISARTAN is contraindicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.**
Hyperkalaemia: During treatment with other medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with MICARDIS		✓	**Different statement:** **Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore not be co-administered with GENERIC TELMISARTAN**
Hepatic impairment: MICARDIS is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. MICARDIS should be used with caution in these patients – see Contraindications. MICARDIS should be used only with caution in patients with mild to moderate hepatic impairment	✓		

MICARDIS®	GENERIC TELMISARTAN		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Active gastric or duodenal ulcer or gastro-intestinal pathologies: Gastro-intestinal adverse events apparently occurred more frequently than with placebo. Gastro-intestinal bleedings have been reported infrequently in clinical trials and this has occurred mainly in patients with baseline gastro-intestinal disease. Therefore, caution should be exercised when administering MICARDIS to this group of patients	✓		
Sorbitol: MICARDIS tablets contains sorbitol and is therefore unsuitable for patients with hereditary fructose intolerance		✓	
Other: As observed for angiotensin converting enzyme inhibitors, MICARDIS and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population. As with any antihypertensive agent, excessive reduction in blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.	✓		
Effects on the ability to drive and use machinery: No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy	✓		
Total Statements: 12	**9**	**3**	**2**

Table 3: Assessing drug information for quetiapine fumarate.

A comparison between SEROQUEL® 25, 100, 200, 300 (Originator brand) and GENERIC QUETIAPINE 25, 100, 150, 200 and 300 (Generic medicine)

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Indications	**Yes**	**No**	
For the treatment of schizophrenia	✓		
For the treatment of manic episodes associated with a bipolar disorder	✓		
Safety and efficacy beyond 12 weeks has not been demonstrated	✓		
Total Statements: 3	**3**	**0**	
Contraindications			
Hypersensitivity to any of the components	✓		
Pregnancy and lactation, as safety has not been established	✓		
Safety and efficacy in children and adolescents have not been demonstrated	✓		
Advanced liver and renal function impairment, as safety has not been demonstrated	✓		
			<u>Additional statements:</u> Quetiapine is not indicated for use in elderly patients with dementia exhibiting behavioural disturbance
			Co-administration with azole antifungals, macrolide antibiotics and HIV protease inhibitors
Total Statements: 4	**4**	**0**	**2**

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Warnings	**Yes**	**No**	
Hyperglycaemia and diabetes mellitus: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL.	✓		
Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics such as SEROQUEL, should be monitored regularly for worsening of glucose control.	✓		
Patients with risk factors for diabetes mellitus who are starting on treatment with atypical antipsychotics as SEROQUEL, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness.	✓		
Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as SEROQUEL, should undergo fasting blood glucose testing.	✓		
In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as SEROQUEL, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of suspect drug.	✓		

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Warnings	**Yes**	**No**	
			<u>Additional statements:</u> **Where the use of GENERIC QUETIAPINE in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances, over sedation and complications associated with hyperglycaemia. Before prescribing GENERIC QUETIAPINE clinicians are advised to carefully assess the risks and benefits of the use of GENERIC QUETIAPINE in elderly patients with dementia as there has been an increase in the cerebrovascular events. In these cases, the risk prediction for stroke in the individual patient must be taken into account**
			GENERIC QUETIAPINE must be used in caution in patients with known cardiovascular disease or other conditions predisposing to hypotension
			GENERIC QUETIAPINE must be discontinued if signs and symptoms of tardive dyskinesia appear

			GENERIC QUETIAPINE must be discontinued and appropriate medical treatment given in case of neuroleptic malignant syndrome
Total Statements: 5	**5**	**0**	**4**
SEROQUEL®	**GENERIC QUETIAPINE**		**Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)**
Interactions	**Yes**	**No**	
Given the primary central nervous system effects of SEROQUEL, SEROQUEL should be used with caution in combination with other centrally acting drugs and alcohol	✓		
The pharmacokinetics of lithium were not altered when co-administered with SEROQUEL	✓		
The pharmacokinetics of sodium valproate and SEROQUEL were not altered to a clinically extent when co-administered	✓		
The pharmacokinetics of SEROQUEL were not significantly altered following co-administration with antipsychotics risperidone or haloperidol	✓		
Co-administration of SEROQUEL and thioridazine caused increase in clearance of SEROQUEL	✓		
SEROQUEL did not induce the hepatic enzyme systems involved in metabolism of antipyrine	✓		

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
In a multiple dose trial in patients to assess the pharmacokinetics of SEROQUEL given before and during treatment with carbamazepine, co administration significantly increases the clearance of SEROQUEL. This increase in clearance reduced systematic SEROQUEL exposure to an average of 13 % of the exposure during administration of SEROQUEL alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, and hence in each patient, consideration for a higher dose of SEROQUEL, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of SEROQUEL is 750 mg/day, for the treatment of schizophrenia, and 800 mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered because of careful consideration of the benefit-risk assessment for an individual patient	✓		**<u>Statement is deleted:</u>** **13 % value not stated**
Co-administration of SEROQUEL with another microsomal enzyme inducer, phenytoin, also caused increases in clearance of SEROQUEL	✓		
Increased doses of SEROQUEL may be required to maintain control of psychotic symptoms in patients co-administered SEROQUEL, phenytoin and other hepatic enzyme inducers. The dose of SEROQUEL may need to be reduced if phenytoin, carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer	✓		

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
CYP3A4 is the primary enzyme responsible for cytochrome P450 medicated metabolism of SEROQUEL.	✓		
The pharmacokinetics of SEROQUEL was not altered following co-administration with cimetidine a known P450 enzyme inhibitor	✓		
The pharmacokinetics of SEROQUEL were not significantly altered following co-administration with the antidepressants imipramine or fluoxetine.	✓		
In a multiple dose trial in healthy volunteers to assess the pharmacokinetics of SEROQUEL given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of SEROQUEL of 235 % and 522 % , respectively, with a corresponding decrease in mean oral clearance of 84 %. The mean half life of SEROQUEL increased from 2,6 to 6,8 hours, but the mean t_{max} was unchanged. Due to the potential for an interaction of similar magnitude in a clinical setting, the dosage of SEROQUEL should be reduced during concomitant use of SEROQUEL and potent CYP34A inhibitors (such as antifungals and macrolide antibiotics)		✓	**<u>Different statement:</u> The co-administration of ketoconazole and GENERIC QUETIAPINE may result in a significant (5-fold) increase in the AUC of GENERIC QUETIAPINE. On the basis of this, concomitant use of GENERIC QUETIAPINE and potent CYP3A4 inhibitors, such as HIV protease inhibitors, azole antifungals and macrolide antibiotics, is contraindicated.**

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
			Additional statements: **GENERIC QUETIAPINE should be used in caution in patients also receiving antihypertensives or medicines that prolong the QT interval**
			GENERIC QUETIAPINE may antagonize the actions of dopaminergics, such as levodopa
13	**12**	**1**	**4**
Dosage and Directions for use			
Twice daily with or without food	✓		
Adults: Treatment of schizophrenia the total dosage for the first 4 days of therapy is 50 mg (day 1), 100 mg (day 2), 200 mg (day 3) and 300 mg (day 4). From day 4 onwards, the dose should be titrated to the effective dose range of 300 - 450 mg/day. However, this may be adjusted, depending on the clinical response and tolerability of the individual patient, within the range 150 – 750 mg/day	✓		
For the treatment of manic episodes associated with bipolar disorder, the total daily dose for the first 4 days of therapy is 100 mg (day 1), 200 mg (day 2),300 mg (day 3) & 400 mg (day 4). Further dosage adjustments up to 800 mg/day by day 6 should be in increments of no greater than 200 mg/day. The dose may be adjusted depending on the clinical response and tolerability of the individual patient, within the range of 200 - 800 mg/day. The usual effective dose is in the range of 400 – 800 mg/day.	✓		

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Dosage and Directions for use	**Yes**	**No**	
Elderly: SEROQUEL should be used in caution in the elderly, especially during the initial dosing period. Elderly patients should be started on 25 mg/day. The dose should be increased daily, in increments of 25 - 50 mg, to an effective dose, which is likely to be lower than that in younger patients.	✓		
Renal & hepatic impairment: The oral clearance of SEROQUEL is reduced by approximately 25% in patients with renal or hepatic impairment. SEROQUEL is extensively metabolized by the liver, and therefore should be used with caution in patients with known hepatic impairment. Patients with renal or hepatic impairment should be started on SEROQUEL 25 mg/day. The dose should be increased daily in increments of 25 - 50 mg, to an effective dose.	✓		
Total Statements: 5	**5**	**0**	**0**
Side Effects			
Nervous system disorders: **Dizziness, somnolence**	✓		
Syncope	✓		
Seizures	✓		
Blood and lymphatic system disorders: **Leucopenia**	✓		
Eosinophilia	✓		
Neutropenia	✓		
Cardiac disorders: **Tachycardia**	✓		
SEROQUEL may cause prolongation of the QTc interval	✓		

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
Gastro-intestinal disorders: **Dry mouth,**	✓		
constipation	✓		
dyspepsia	✓		
General disorders and administration site conditions: **Asthenia**	✓		
peripheral oedema	✓		
Neuroleptic malignant syndrome	✓		
Investigations: **Weight gain, elevations in serum transaminases Elevations in gamma-GT levels, elevations in non-fasting serum triglycerides levels, elevations in total cholesterol**	✓		
Respiratory, thoracic and mediastinal disorders: **Rhinitis**	✓		
Vascular disorders: **Orthostatic hypotension**	✓		
Immune system disorders: **Hypersensitivity (angioedema, anaphylaxis, uticaria/rash)**	✓		
Others: **Fever**	✓		
Reproductive system and breast disorders: **Priaprism**	✓		

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
SEROQUEL treatment was associated with dose-related decrease in thyroid hormone levels particularly total T4 and free T4. The reduction in total and free T4 was maximal within the first two weeks of treatment with no further reduction during long term treatment, with no further reduction during long term treatment. There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on the total and free T4 irrespective of the duration of the treatment. Smaller decreases in total T3 and reverse T3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with any indication that SEROQUEL causes clinically relevant hypothyroidism.	✓		
headache	✓		
Abdominal pain	✓		
Back pain	✓		
Chest pain	✓		
hypertension	✓		
diarrhoea	✓		
mylagia	✓		
Dry eyes	✓		
Ear pain	✓		
Urinary tract infection	✓		

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
Extrapyramidal symptoms occur at an incidence similar to placebo and are not dose related.		✓	
			<u>Additional statements:</u> **Nervous system disorder anxiety, extrapyramidal symptoms, tardive dyskinesia**
			Metabolism and nutritional disorder: Hyperglycaemia, diabetes mellitus
			Blood and lymphatic system disorder Thrombocytopenia, Agranulocytosis
			General disorders and administration site conditions: **withdrawal symptoms**
			Vascular disorders **Venous thromboembolism**
			Immune system disorders: Steven-Johnson syndrome
			Reproductive system and breast disorders: galactorrhoea
			Psychiatric disorders: Frequent: Abnormal dreams, nightmares
			Hepatobiliary disorders: Jaundice, hepatitis
			Eye disorders: asymptomatic changes in the lens of the eye with long-term treatment, blurred vision
Total Statements: 32	**31**	**1**	**10**

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Concomitant illness: SEROQUEL should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension	✓		
SEROQUEL may induce orthostatic hypotension, especially during initial dose-titration period, this is more common in elderly patients than in younger patients	✓		
In clinical trials SEROQUEL was not associated with a persistent increase in QTc intervals. However, caution should be exercised when SEROQUEL is prescribed with drugs known to prolong QTc interval, especially in the elderly.	✓		**<u>Statement is deleted:</u>** **In clinical trials SEROQUEL was not associated with a persistent increase in QTc intervals.**
Seizures: Caution is recommended when treating patients with a history of seizures	✓		
Tardive dyskinesia: There is a potential for SEROQUEL to cause tardive dyskinesia. If all signs and symptoms of tardive dyskinesia appear, discontinuation of SEROQUEL should be considered.	✓		
Neuroleptic malignant syndrome: has been associated with SEROQUEL treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability and increased creatinine phosphokinase. SEROQUEL should be discontinued and appropriate medical treatment given.	✓		

SEROQUEL®	GENERIC QUETIAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Effect on ability to drive and use machines: GENERIC QUETIAPINE may cause somnolence which may interfere with activities requiring mental alertness. Patients should be advised not to operate hazardous machines, or drive vehicles, until individual susceptibility is known.	✓		**<u>Additional statements:</u>** **Withdrawal recommendation: It is recommended that GENERIC QUETIAPINE be gradually withdrawn because of the risk of withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses with abrupt cessation. Recurrence of psychotic symptoms may also occur and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesis) have been reported**
			Lactose: GENERIC QUETIAPINE contains lactose. Patients with hereditary galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take GENERIC QUETIAPINE
Total Statements: 7	**7**	**0**	**3**

Table 4: Assessing drug information for olanzapine.

A comparison between ZYPREXA® 2,5, 5 and 10 mg (Originator brand) and GENERIC OLANZAPINE 2,5, 5 and 10 mg (Generic medicine)

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Indications	**Yes**	**No**	
For the management of the manifestations of psychotic disorders	✓		
The antipsychotic efficacy of ZYPREXA® was established in controlled trials of schizophrenia in patients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech)	✓		**Part of the statement is deleted:** "in controlled trials of"
It is recommended that responding patients be continued on ZYPREXA® at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment	✓		
ZYPREXA® is also indicated for the treatment of an acute episode of moderate to severe mania and for preventing recurrence of manic or depressive episodes of bipolar disorder	✓		
Total statements: 4	**4**	**0**	**1**
Contraindications			
In patients who are hypersensitive to the product	✓		
In patients with known risk of narrow angle glaucoma	✓		
Paediatric use: Safety and efficacy in patients under 18 years of age have not been established	✓		
Total Statements: 3	**3**	**0**	**0**

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Warnings	**Yes**	**No**	
Discontinuation reactions may occur usually within a week of discontinuing ZYPREXA®. These reactions may consist of a cholinergic syndrome (diaphoresis, diarrhoea, sialorrhea, nausea and vomiting, anxiety, agitation, insomnia and tremor). ZYPREXA® should therefore be gradually discontinued.	✓		
Hyperprolactinaemia: ZYPREXA® elevates prolactin levels and a modest elevation persists during chronic administration. An increase in mammary gland neoplasms has been found in rodents after chronic administration of antipsychotic medicines and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumours in rodents is unknown	✓		**<u>Part of the statement is deleted:</u>** **"An increase in mammary gland neoplasms has been found in rodents after chronic administration of antipsychotic medicines and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumours in rodents is unknown"**
Neuroleptic malignant syndrome (NMS): NMS has occurred infrequently in association with ZYPREXA®. NMS is a potentially fatal symptom complex. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental state, autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, cardiac dysrhythmia). Additional symptoms may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. ZYPREXA® should be discontinued should any of the clinical manifestations of NMS or high fever without additional clinical manifestations of NMS be observed	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Warnings	**Yes**	**No**	
Seizures: ZYPREXA® should be used cautiously in patients who have history of seizures or are subject to factors which may lower seizure threshold. Seizures have been reported to occurring infrequently in patients treated with olanzapine. In most of these cases, a history of seizures or risk factor for seizures was reported	✓		
Tardive dyskinesia: ZYPREXA® was associated with a low incidence of treatment emergent dyskinesia. If signs or symptoms of tardive dyskinesia appear in a patient on ZYPREXA®, a dose reduction or discontinuation of treatment should be considered. However, some patients may benefit from continued treatment with ZYPREXA® despite the presence of the syndrome. The risk of tardive dyskinesia increases with long term exposure and symptoms can temporarily deteriorate or even arise after discontinuation of treatment.	✓		**<u>Part of the statement is deleted:</u>** **"However, some patients may benefit from continued treatment with ZYPREXA® despite the presence of the syndrome."**
Hepatic impairment: Caution should be exercised in patients with signs and symptoms of hepatic impairment. in patients with pre-existing conditions associated with limited hepatic functional reserve and in patients who are being treated with potentially hepatotoxic medicines. Periodic assessment of transaminases is recommended in patients with significant hepatic disease. A 5 mg starting dose should be considered for patients with moderate hepatic impairment.	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Warnings	**Yes**	**No**	
Safety experience in elderly patients with dementia-related psychosis: In elderly patients with dementia-related psychosis, the efficacy of ZYPREXA® has not been established. In placebo- controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3,5 % vs 1,5 %, respectively). Abnormal gait and falls were very common (> 10 %), urinary incontinence and respiratory infection were common, and there was an increased incidence in cerebrovascular incidents, including stroke. Risk factors that may predispose this patient population to increased mortality when treated with ZYPREXA® include age ≥ 80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration)	✓		**<u>Additional Statement:</u> Caution should be exercised in the elderly, especially if there are other factors that might additively influence medicine metabolism and/or pharmacodynamic sensitivity**
Hyperglycaemia and diabetes mellitus: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients with ZYPREXA®. Patients with an established diagnosis of diabetes mellitus who are started on ZYPREXA® should be monitored for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes), who are starting treatment with ZYPREXA® should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with ZYPREXA® should undergo fasting glucose testing. In some cases, hyperglycaemia was resolved when ZYPREXA® was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug	✓		
Total Statements: 8	**8**	**8**	**3**

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
Given the primary CNS effects of olanzapine, caution should be exercised when ZYPREXA® is taken in combination with other centrally acting agents (especially those that can cause CNS depression) and alcohol	✓		
As it exhibits in vitro dopamine antagonism, ZYPREXA® may antagonize the effects of levodopa and dopamine agonists	✓		
Because of the potential for inducing hypotension, ZYPREXA® may enhance the effects of certain antihypertensive agents	✓		
In clinical trials with oral administration, olanzapine was not associated with a persistent increase in absolute OT intervals. Only 8 of the 1685 subjects had increased QTc interval on multiple occasions. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients when congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesemia.)	✓		**<u>Part of the statement is deleted:</u>** **"In clinical trials with oral administration, olanzapine was not associated with a persistent increase in absolute QTc intervals. Only 8 of the 1685 subjects had increased QTc interval on multiple occasions"**
Caution should be exercised in patients who received treatment with medicinal products that can lower blood pressure by mechanisms other than α-1 adrenergic antagonism	✓		
Potential interactions affecting olanzapine: Since olanzapine is metabolized by CYP1A2, substances that can significantly induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine.	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
Potential for other medicines to affect ZYPREXA®: Single doses of antacids (aluminium, magnesium) or cimetidine did not affect the oral bioavailability of olanzapine. However, the concomitant administration of activated charcoal reduced the bioavailability of oral olanzapine by 50 to 60 % and should be taken at least 2 hours before or after olanzapine.	✓		
Fluoxetine (60 g dose or 60 mg daily for 8 days) in combination with olanzapine (5mg single dose), causes a mean 16 % increase in the maximum concentration of olanzapine and a mean 16 % decrease in olanzapine clearance. The effect of repeat dosage of ZYPREXA® and higher dosages has not been evaluated. Combination therapy is not advised.	✓		**<u>Different statement:</u> Fluoxetine – in combination with GENERIC OLANZAPINE may cause an increase in the maximum concentration of olanzapine and a decrease in olanzapine clearance. The effect of repeat dosage of GENERIC OLANZAPINE has not been evaluated. Combination therapy is not advised.**
Induction of CYP1A2: The metabolism of olanzapine may be induced by concomitant smoking or carbamazepine therapy causing subsequent slightly to moderately lower olanzapine plasma levels. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine may be considered if necessary.	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
Inhibition of CYP1A2: Known potent inhibitors of CYP1A2 activity may decrease olanzapine clearance. Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine C_{max} following fluvoxamine was 54 % in female non-smokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin or ketoconazole. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 Is initiated.	✓		**<u>Part of the statement is deleted:</u>** **"The mean increase in olanzapine C_{max} following fluvoxamine was 54 % in female non-smokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively."**

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Interactions	**Yes**	**No**	
Potential for ZYPREXA® to affect other medicines: Olanzapine may antagonize the effects of direct and indirect dopamine agonists. In clinical trials with single doses of ZYPREXA®, no inhibition of the metabolism of imipramine/desipramine (P450-CYP2D6 or P450-CYP3A/1A2), warfarin (P450-CYP2C9), theophylline (P450-CYP1A2) or diazepam (P450-CYP3A4 and P450-CYP2C19) was evident. ZYPREXA® showed no interaction when co-administered with lithium or biperiden. Also, in in vitro studies with human liver microsomes, olanzapine showed little potential to inhibit cytochromes P450-CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Given the extensive clinical and in vitro studies, ZYPREXA® would not be expected to interfere with the metabolism of most medicines. Studies in vitro using human liver microsomes, determined that ZYPREXA® has little potential to inhibit the glucoronidation of valproate, the major metabolic pathway for valproate. Further, valproate was found to have little effect on the metabolism of ZYPREXA® in vitro. Daily concomitant in vivo administration of 10 mg olanzapine for 2 weeks did not affect steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.		✓	**<u>Part of the statement is deleted and different:</u> No inhibition of the metabolism of imipramine/desipramine (P450-CYP2D6 or P450-CYP3A/1A2), warfarin (P450-CYP2C9), theophylline (P450-CYP1A2) or diazepam (P450-CYP3A4 and P450-CYP2C19) is evident. GENERIC OLANZAPINE does not interact when co-administered with lithium or biperiden.**
Total statements: 11	**10**	**1**	**4**

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Dosage and Directions for use	**Yes**	**No**	
Psychotic disorders: ZYPREXA® tablets should be administered on a once a day schedule without regards to meals, generally beginning with an initial dose of 5 to 10 mg/day, with a target dose of 10 mg/day within several days	✓		
In order to evaluate efficacy and guard against side-effects, dosage increases should not be considered before one week, since steady state for olanzapine would not be achieved for approximately one week. The dose range is from 5 mg to 20 mg per day. Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment	✓		
Acute mania in bipolar disorder: initial dose: ZYPREXA® should be administered on a once a day schedule without regard to meals, generally beginning with 10 mg. Dosage adjustments within the dose range of 5 mg to 20 mg, if indicated, should not occur at intervals of not less than 24 hours.	✓		
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg per day. For patients who have been receiving ZYPREXA® for treatment of manic episode, continue therapy for preventing reoccurrence at the same dose. **An increase to a greater dose than the recommended starting dose, within the range of 5 mg to 20 mg per day, is advised only after appropriate clinical assessment and should generally occur at intervals of not less than 24 hours. The safety of doses above 20 mg/day has not been evaluated in clinical trials. Gradual tapering of the dose should be considered when discontinuing ZYPREXA®.**	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Dosage and Directions for use	**Yes**	**No**	
			<u>Additional Statement:</u> **Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment. A 5 mg starting dose should be considered for patients with hepatic impairment and may also be considered for the elderly patient. The safety of doses above 20 mg/day has not been evaluated in clinical trials. Improvement in the patient's clinical condition may take several days to weeks. Patients should be closely monitored during this period.**
Total Statements: 4	**4**	**0**	**1**
Side Effects			
Body as a whole: **Allergic reaction, Discontinuation reaction**	✓		
Asthenia	✓		
Photosensitivity reaction	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
Core side-effects identified only during bipolar mania clinical trials in patients receiving olanzapine in combination with lithium or valproate: ***Body as a whole:*** **Very common: Weight gain**	✓		
Cardiovascular: **Bradycardia**	✓		
Orthostatic hypotension	✓		
Venous thromboembolism		✓	
Digestive system: **Common: Constipation** **Very rare: Hepatitis, pancreatitis** ***Core side-effects identified only during bipolar mania clinical trials in patients receiving olanzapine in combination with lithium or valproate:*** ***Digestive system:*** **Very common: Dry mouth, Increased appetite**	✓		
Haematologic: **Leucopenia** **Thrombocytopenia**	✓		
Metabolic: **Diabetic coma, Diabetic ketoacidosis, Hypercholesterolaemia, Hyperglycaemia, Hypertriglycericaemia** **Peripheral oedema**	✓		**<u>Additional Statement:</u>** **Metabolic and nutritional disorders: development or exacerbation of diabetes** **<u>Deleted Statement:</u>** **Hypercholesterolaemia**

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
Musculoskeletal: **Rhabdomyolysis**	✓		**<u>Additional Statement:</u>** **Classified as musculoskeletal, connective tissue and bone disorders: Extremity pain (other than joint), joint pain, back pain**
Nervous system: **Akathisia, Dizziness** **Seizures** **Somnolence**	✓		
Core Side-effects identified only during clinical trials in patients with dementia of the Alzheimer's type: ***Nervous system:*** **Very common: Abnormal gait, Falls**	✓		
Core side-effects identified only during clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease: ***Nervous system:*** **Very common: Hallucinations, Parkinsonian symptomatology**	✓		**<u>Deleted statement:</u>** **Hallucinations**
Core side-effects identified only during bipolar mania clinical trials in patients receiving olanzapine in combination with lithium or valproate: ***Nervous system:*** **Common: Speech disorder** **Very common: Tremor**	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
Urogenital system: **Very rare: Priapism** **Core Side-effects identified only during clinical trials in patients with dementia of the Alzheimer's type:** ***Urogenital system:*** **Common: Urinary incontinence**	✓		**Additional Statement:** **classified as reproductive system and breast disorders: premenstrual syndrome** **Deleted Statement:** **Urinary incontinence**
Skin and appendages: **Rare: Rash**	✓		**Additional Statement:** **classified as:** **Skin and subcutaneous disorders: alopecia**
Laboratory analytes: ***Clinical chemistry:*** **Common: ALT/SGPT – Increased, AST/SGOT – Increased** **Very common: Prolactin - increased**	✓		**Additional Statement:** **Classified as hepato-biliary disorders: jaundice**
Hematology **Common: Eosinophilia**	✓		**Additional Statement:** **Classified as blood and lymphatic system disorders: neutropenia**
Core Side-effects identified only during clinical trials in patients with dementia of the Alzheimer's type: ***Respiratory system:*** **Pneumonia**			**Additional Statement:** **Classified as frequent and as respiratory, thoracic and mediastinal disorders: Rhinitis, cough, pharyngitis**

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Side Effects	**Yes**	**No**	
			Additional statements: **Psychiatric disorders: personality disorder, amnesia, anxiety, euphoria, hostility**
			Nervous system disorder: headache, agitation, nervousness, myoclonus, extrapyramidal effects, dystonia, dyskinesia, movement disorder, articulation impairment, hypertonia, neuroleptic malignant syndrome, tardive dyskinesia
			Eye disorders: less frequent: Amblyopia, blepharitis, corneal lesion
			Cardiac disorders: **Chest pain, tachycardia, changes in ECG parameters, ventricular tachydysrhythmias**
			Vascular disorders: hypotension, peripheral odema
			Gastrointestinal disorders: abdominal pain

			General disorders and administration site conditions: Fever, intentional injury
			Investigations:, high creatine phosphokinase, decreased erythrocyte count, hematocrit, haemoglobin, leucocyte count, lymphocytes, thrombocytes and platelets, increased MCHC, monocytes and eosinophils, decreased bicarbonate, calcium phosphorous, albumin and total protein, increased chloride, GGT and phosphorous
Total Statements: 20	**19**	**1**	**17**
ZYPREXA®	**GENERIC OLANZAPINE**		**Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)**
Special precautions	**Yes**	**No**	
During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period	✓		
Concomitant illnesses: Clinical experience with ZYPREXA® in patients with concomitant illnesses is limited. As ZYPREXA® demonstrated anticholinergic activity in vitro, caution is advised when prescribing for patients with symptomatic prostate enlargement, narrow-angle glaucoma or paralytic ileus and related conditions.	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
ZYPREXA® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from pre-marketing clinical studies. Because of the risk of orthostatic hypotension with ZYPREXA®, caution should be observed in cardiac patients.	✓		
There is an increased prevalence of diabetes amongst patients with schizophrenia. As with other antipsychotics, hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during ZYPREXA® treatment. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for developing diabetes mellitus.	✓		
Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia: Cerebrovascular adverse events (e.g. stroke, transient ischemic attack), including fatalities, were reported in trials of ZYPREXA® in elderly patients with dementia-related psychosis. In placebo-controlled studies, there was a higher incidence of CVAE in patients treated with ZYPREXA® compared to patients treated with placebo (1,3 % vs 0,4 %, respectively). All patients who experienced a cerebrovascular event had pre-existing risk factors known to be associated with an increased risk for a CVAE (e.g. history of previous CVAE or transient ischemic attack, hypertension, cigarette smoking) and presented with concurrent medical conditions and/or concomitant medications having a temporal association with CVAE. ZYPREXA® is not approved for the treatment of patients with dementia-related psychosis.	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Effect on ability to drive and use machines: ZYPREXA® may cause somnolence. Patients should e cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that ZYPREXA® therapy does not affect them adversely.	✓		
Geriatric use: In clinical studies, in general, there was no indication of any different tolerability of ZYPREXA® in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to ZYPREXA®, should lead to consideration of a lower starting dose. As postural hypotension was infrequently observed in the elderly in clinical trials, it is recommended that blood pressure is measures periodically in patients over 65 years.	✓		**Part of the statement is deleted:** **". As postural hypotension was infrequently observed in the elderly in clinical trials, it is recommended that blood pressure is measures periodically in patients over 65 years."**

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Orthostatic hypotension: ZYPREXA® may induce orthostatic hypotension associated dizziness, tachycardia and in patients, syncope, especially during initial treatment period.	✓		**<u>Additional statement:</u> Plasma clearance of olanzapine is higher in smokers. The combined effects of age, smoking and gender could lead to substantial pharmacokinetic differences. The clearance in young smoking males, for example, may be 3 times higher than that in elderly non-smoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine**
Transaminase elevations: Transient elevations of liver transaminases (ALT, AST) have been observed. Caution should therefore be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve and in patients who are being treated with potentially hepatotoxic agents. In the event of elevated ALT and/or AST during treatment, follow-up should be organized and dose reduction should be considered. In cases where hepatitis has been diagnosed, olanzapine treatment should be discontinued.	✓		

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Haematology: Caution should be exercised when using olanzapine in the following types of patients: **- Low leucocyte and/or neutrophil counts due to any reason** **- History of medicine induced bone marrow depression/toxicity** **- bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy** **- Hypereosinophilic conditions or with myeloproliferative disease** **Thirty-two patients with clozapine-related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts.**	✓		**<u>Part of the statement is deleted:</u>** **"Thirty-two patients with clozapine-related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts."**
Body temperature regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ZYPREXA® for patients who will be experiencing conditions which may contribute to an elevation in core body temperature.	✓		
Dysphagia: Oesophageal dysmotility and aspiration have been associated with antipsychotic medicines. ZYPREXA® should be used with caution in patients at risk for aspiration pneumonia.	✓		
Suicide: The possibility of suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany ZYPREXA® treatment.	✓		
Carcinogens: Based on the results of studies in mice and rats it was concluded that olanzapine is not carcinogenic.		✓	
Mutagenesis: Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and in vitro and in vivo mammalian tests.		✓	

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
Impairment of fertility: In rats, male mating, but not fertility, was impaired. Discontinuation of olanzapine treatment reversed the effect on mating performance. In female rats, oestrus cycles and reproduction parameters were influenced at doses higher than the maximum human dose.		✓	
			<u>Additional statement:</u> **Lipid alterations:** **Undesirable alterations in lipids have been observed in patients with low leucocyte and/or neutrophil counts due to any reason, patients with a history of medicine-induced bone marrow depression/toxicity, patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy, and in patients with hypereosinophilic conditions or with myeloproliferative disease**

ZYPREXA®	GENERIC OLANZAPINE		Any deletions, additions or different statements that are present in the generic medicine package insert (GPI) and not in the originator brand package insert (OPI)
Special precautions	**Yes**	**No**	
			Lactose: GENERIC OLANZAPINE tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take GENERIC OLANZAPINE.
			Lecithin soya: GENERIC OLANZAPINE tablets contain lecithin soya. Patients who are allergic to peanut or soya, should not take GENERIC OLANZAPINE.
Total Statements: 16	**13**	**3**	**6**

Appendix B: Probe Questions (use as guide only)

- What sources of information do you use when compiling a package insert for a generic medicine?
- What information do you extract from each of the above sources?
- Of the sources mentioned above, which is the main source of information used?
- Are there any other sources of information that you use when compiling a package insert for a generic medicine other than those mentioned in Question 1?
- From where do you obtain the clinical data presented in the generic package insert?
- How is the clinical data validated?
- Do you use the guidelines provided by the Medicines Control Council to compile the generic medicine package insert?
- Do you find the guidelines useful and are they easy to interpret?
- Do you find there to be any discrepancies or grey areas that could be improved on or clarified further?
- When compiling a package insert for a generic medicine do you take into account any information that is available globally?
- Do you find that sometimes the information being presented in the generic medicine package insert to be more recent than that presented in the brand name medicine package insert?
- How do you experience the current system of package insert registration? What challenges do you face?
- What challenges do you face when having to update a package insert? Can you update a package insert during the registration process?
- If you could make changes to the system, what would you do? How would go about doing it?
- Do you think we should be looking at the international guidelines? What would be the benefits of considering international guidelines?
- Is there a mechanism to raise concerns or matters of interest with the health authority?
- Do you think that the regulator/evaluator has an impact on the approval process of the package insert? Please elaborate.
- Do you believe that there may be instances where you feel that you have to compromise on the content or the way in which information would be included in order to be able to get the package insert through the registration process successfully?
- What do you believe are the reasons for the similarities and differences noted in selected package inserts?
- How has the process of approval of the package insert impacted the company?
- Which areas of the package insert compilation lead to frustration?
- Is there any additional comments that you would like to add?

Appendix C: HREC Clearance Certificate

R14/49 Ms Shaistha Sing

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160861

NAME: (Principal Investigator)	Ms Shaistha Sing
DEPARTMENT:	Pharmacy and Pharmacology Mylan (Pty) Ltd
PROJECT TITLE:	A Comparison of the Package Inserts of Originator Brands and Generic Medicines Registered at an International Pharmaceutical Company
DATE CONSIDERED:	26/08/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/02/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

22/02/2017
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D: Title Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

10 January 2018
Person No: 840298
PAG

Ms S Sing
The Kennedy Unit 17 Block 2
Mercurius Street
Solheim
1401
South Africa

Dear Ms Sing

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *A comparison of the package inserts of originator brands and generic medicines registered at an international pharmaceutical company* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix E: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Shaistha Sing (Student number: 840298) am a student registered for the degree of Master of Science in Medicine (Regulatory Affairs) in the academic year 2018.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 9/9/2018

Explanation of the percentage received from the Turnitin report

The study compared the information contained in originator and generic package inserts. The information was taken verbatim, directly from the PIs and hence the percentage seen on the Turnitin report is recorded as high i.e. 25 %.

Attachment 1 reflects the Turnitin report that was generated with all the tables that include the information that was included directly from the PIs. The similarity index is recorded as 25 %.

Attachment 2 reflects the Turnitin report that was generated with the removal of all the tables that include the information that was included directly from the PIs. The similarity index is recorded as 10 %.

It can therefore be demonstrated that the high quantity of information extracted directly from the PIs, for the textual comparison is the cause for the high percentage observed in the Turnitin report.

Attachment 1

Turnitin Originality Report

Processed on: 09-Sep-2018 12:59 PM SAST
ID: 998875813
Word Count: 19050
Submitted: 1

840298:report_with_tables.docx By Shaistha Sing

Similarity Index	Similarity by Source	
25%	Internet Sources:	21%
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CHAPTER 1: INTRODUCTION 1.1 Context for this study Access to medicine for the treatment of illnesses is an essential component of any healthcare system. Many people need to take medication on a daily basis. South Africa's health care system faces many challenges and hence the system struggles to function as optimally as it could (Mayosi, Fisher, Lalloo, Sitas, & Tollman, 2009). The high cost of medicine remains a barrier for most of the South African population (Bangalee, 2015). One area in health care that has been identified to improve access is the use of generic substitution practices which has been identified as a mechanism that can contain costs (Karim, Pillai, Ziqubu-Page , Cassimjee, & Morar, 1996). This has been supported by legislation that allows for the generic substitution of originator medicines with generic medicines, on condition that the substitution is permitted by the patient (Bangalee, 2015). But, the availability of generic medicines does come with its own set of potential problems which create doubt and a lack of confidence with the use of generic medicines. This research aims to describe some of the problems that have been identified with the use of generic medicine with a focus on the PIs that are contained in the carton of a generic medicine. The findings of this study provide information that can assist with improving the access and acceptance of generic medicines. 1.1.1 Generic medicines A generic medicine is defined by the World Health Organization (WHO), as "a pharmaceutical product, usually intended to be interchangeable with an originator product. The generic medicine is manufactured without a license from the originator company and marketed after the expiry date of the patent or other exclusive rights" (Alrasheedy, et al., 2014). While originator medicines must conform to strict safety, quality and efficacy measures prior to obtaining health authority approval, generic medicines must only prove quality and bioequivalence to the originator medicine. Thus, the requirements for a generic medicine are less stringent than those for the new chemical entity, and the costs of testing and launching a generic medicine are a fraction of research and development costs of originator medicines. Medicinal products are considered to be bioequivalent if, after they are administered in the same dose, the rate and extent of bioavailability and the effects with respect to safety and efficacy are the same as the originator. There is no need for companies applying for registration of generic medicine to repeat the clinical trial studies that were submitted for registration of the originator medicine. This is one of the reasons why generic medicines are available at a cheaper price than the originator medicine (Dunne, Shannon, Dunne, & Cullen, 2013). Generic medicines have the same active ingredient, dosage form, strength and route of administration as the originator medicine and thus the information gathered is applicable to the generic. 1.1.2 Generic medicine labelling The primary source of drug information used in South Africa is the approved medicine PI. Generic pharmaceutical companies extract the safety and efficacy information directly from the PI of the originator medicine. Hence the information with respect to safety and efficacy provided in the PI of the generic medicine should be consistent with that provided in the originator medicine PI. The PI is a document that accompanies a medicine. It is intended to contribute to the safe and efficacious use of a medicine. It includes a scientific explanation of the uses for the medicine and its limitations which has been established by supporting data. It should be written in a manner that is not promotional, false or misleading. The information should be evidence based and updated from time to time as relevant pre-clinical and clinical data becomes available (Deepak, et al., 2013). The PI must be written in a manner that is clear and so that it can be understood by the general population (Al-Ramahi, Zaid, Kettana, Sweileh, &Al- Jabi, 2012). PIs are used as the primary source of medicine information by both the prescribers and the patient. Sometimes non-compliance in taking medication is because patients misunderstand instructions given by health care professionals. PIs then become a useful tool which conveys the verbal message (Morris & Halperin, 1979). However, some research has shown that PIs may impact patient compliance in an undesirable manner if the information that is provided is unreliable and incomplete (Dutta, Mahato, Saha, & Bhattacharyya, 2014). Incomplete and unreliable information could result in inconsistent prescribing patterns and may have a negative impact on patient safety and overall healthcare (Gharibyar, Sharif, Ghandour, Saffarini, & Aden, 2013). 1.1.3 Approval of Package inserts by the South African Health Authority Generic medicine can only be registered if it has met all the necessary standards as set out in the guidelines published by the local regulatory body (Sawalha, Sweileh, Zyoud, & Jabi, 2008). These include products that are of a high quality, and that is efficacious and safe for use in the intended population (Alrasheedy, et al., 2014). The South African Health Products Regulatory Authority (SAHPRA), previously known as the Medicines Control Council (MCC) has the task of evaluating and approving the information provided in the package insert (PI). This procedure takes place before the registration of the product. Once the PI has been approved, it cannot be changed unless

approval from SAHPRA has been granted. The Medicines and Related Substances Act (Act no. 101 of 1965) and the general regulations made in terms of the Medicines and Related Substances Act (Act no. 101 of 1965), address the legal requirements that a PI be supplied with every medicine. Regulations 9 and 10 of Act 101 stipulate the minimum information requirements of the PI. Although the type of information provided under specific headings in the PI is mandated by SAHPRA, the process of compiling a PI or amending a PI is not always clear. The regulatory authority plays a key role in determining the contents of the PI however many health authorities, including SAHPRA have challenges that include limited human resources with skills oversight and system insufficiencies (MCC/MRA Backlog Task Team, 2010). 1.2 Literature review Whilst there has been some research conducted on PIs internationally, very little research has been done in South Africa. International and local research primarily focuses on the differences that have been noted in the various brands of generic medicine PIs (Filby, 2008). 1.2.1 International research Research that has been conducted internationally shows the following: The information in PIs is a source of information for patients which contributes to the safe and effective use of the medicine. However, this information is often lacking in consistency, completeness and is sometimes difficult to read and understand. An article published by Shrank and Avorn (2007), explored the potential and limitations of written drug information. Sources of written information available in the United States and the regulations that control the content of information were reviewed. Evidence shows that whilst patients prefer to receive medical information from health care providers, this is not actually what happens. The interaction between health care provider and patient is often inadequate. Patients often do not remember what was discussed and seek written information on how to use their medicine. An observation of medicine labelling showed that there was a lot of variability in the provided consumer medicine information (Shrank & Avorn, 2007). Prescribing materials from pharmaceuticals of the same drug within even one country was also found to show considerable differences. In 2003, Reggi et al conducted an international comparative study of different brands of the same drug in 26 countries (including America, Europe, Africa, Asia and Australasia). Three widely used drugs were selected: ciprofloxacin, fluoxetine and nifedipine. Results revealed that only two countries reflected all the indications for ciprofloxacin, three countries for fluoxetine and eleven for nifedipine. No countries reflected all the major side effects for nifedipine and fluoxetine and only one country reflected all the side effects for nifedipine. No countries listed all the precautions (Reggi, et al., 2003). Page 4 of 73 While the indications for a medicine may be different across countries there should be little difference in the listed warnings, precautions and contraindications. However, research has shown that this is not always the case. Pfistermeister et al (2013) conducted an in-depth comparison of the approved German, Swiss, British and US- American prescribing information of the top 10 prescribed psychiatric drugs. The comparison revealed that was a lot of variability in the important information across all the investigated markets. Health care providers who prescribe the same drug for the same medical condition in different countries are presented with different indications, warnings and special precautions or contraindications. When comparing the current medicine registration system in South Africa to other medicine registration systems in the world it becomes apparent that there are gaps in the current system being used by SAHPRA. The current medicine registration system in South Africa includes the issue of a product registration certificate once the health authority is satisfied that the medicine is proven to be safe, of good quality and is efficacious. The system does not include the provision of any additional public reports that provide information about the considerations that led the regulator to approve or refuse the application. As part of the European Medicines Agency (EMA) and the Therapeutic Goods Administration (TGA) commitment to transparency, public assessment reports are provided upon completion of the review of a medicine (Papathanasiou, et al., 2016). Transparency and communication between the pharmaceutical company and the health authority during the approval process of medicine is crucial. The EMA guidance documents stipulate specific timelines for evaluation of a medicine application (Kashyap, Gupta, & Ragunandanh, 2013). Currently in South Africa there are no published timelines for registration. The lack of timelines would mean that a medicine could be in the registration process for many years before obtaining approval. This also leads one to believe that there is no accountability on the part of the regulator and that medicines would not be registered as efficiently as they are in other parts of the world. South Africans would thus wait longer to have access to the same medicines that may already be available in other countries. Page 5 of 73 1.2.2. Local research Guidelines established by the South African health authority primarily focuses on the structure and content of the information provided under the different headings in the PI. There is very little guidance on the process of compilation that is to be followed and the sources of information to be used for the compilation of a generic medicine PI. The consequence of the lack of prescription in the documents results in regulatory pharmacists having to compile PIs differently using their years of experience in regulatory affairs as a guiding tool. In South Africa, negative perceptions exist surrounding the use of generic medicines (Patel, Gauld, Norris, & Rades, 2012). Research conducted by Patel et al (2012) explains that the perceptions of health care providers and patient consumers about the quality of generic medicines contributes to a lack in confidence in using them. Mohlala et al (2010) showed that the rate of prescribing drugs by their generic name in public and private health care facilities in 2 provinces in South Africa was as low as 45.2% in the public hospital and 24.5% by GPs (Mohlala, Peltzer, Phaswana-Mafuya, & Ramlagan, 2010). Whilst generic medicines are available in South Africa, patients and health care providers will only use them if they are confident in their safety, efficacy and quality. Two recent studies were conducted on generic medicine PIs in South Africa (Aziz 2017; Moodley 2016). The study that was carried out in 2016, concluded that PIs of approved products that are currently circulating show considerable differences between the originator product and subsequent generic brands of the same drug substance (Moodley, 2016). Another recent study that was carried out in 2017 evaluated the congruency of information in the patient information leaflet (PIL) as compared to the PI of 6 selected antihypertensive drugs. The study revealed a lack of congruency of key information (Aziz, 2017). This research adds to the small body of local research and provides insight into the differences noted between the PIs of originator and generic medicines; sources of information used by regulatory pharmacists, the regulatory process followed and the experiences gained during the compilation of a generic medicine PI for approval by the South African Health Product Regulatory Authority. 1.3 Problem statement The approval process for generic medicines is set at a lower threshold to enable generic companies to introduce drugs at affordable rates. The PI would be expected to mirror the originator PI as the generic company does not have the obligation to run clinical trials on efficacy and safety. But the timeline for registration in South Africa is long and contributes to a significant delay in access to generic medicines (Bateman, 2010). The processes followed for the compilation, assessment and approval of a generic medicine PI in South Africa is unclear. Previous research has identified inconsistencies in the information contained in PIs across brands of the same medicines (Pfistermeister, et al., 2013). These create doubt and a lack of confidence regarding the use of generic medicines. The findings of this study could contribute in assisting SAHPRA to amend and formulate better policies to regulate and approve generic medicine PIs. This will also aid in the better functioning of the pharmaceutical industry's regulatory departments. 1.4 Study aim and Objectives The aim of the study is to compare the PIs of originator and generic medicines of a small sample of medicines registered in South Africa and to determine the sources of information that are used to compile the generic medicine PI. The study also aims to explain the regulatory process followed by a pharmaceutical company to obtain approval of a generic medicine PI in South Africa. The objectives of the study are ? To describe the core differences between originator medicine PIs and generic medicine PIs with respect to the listed indications, contraindications, warnings, interactions, dosage and directions for use, side-effects and special precautions. ? To identify the process and the sources of information that regulatory personnel from one pharmaceutical company use to compile the generic medicine PI. ? To explore the experiences and perceptions of the regulatory staff from this pharmaceutical company with regard to compiling generic PIs for approval by SAHPRA. CHAPTER 2: METHODS 2.1 Introduction The study was conducted in two phases and a qualitative design was used. Qualitative research methods were used because they enabled the researcher to identify inconsistencies in the PIs through a textual analysis. Qualitative methods were appropriate to identify, describe, and understand the regulatory processes used by pharmacists at a specific pharmaceutical company. The regulatory processes involved in the compilation of a generic medicine PI includes the identification of the sources of information that are used and experiences that were gained during the compilation of a medicine PI. This chapter discusses the methods that were utilized to conduct this study. 2.2 Research site The pharmaceutical company that was selected as the research site is one of the world's leading generics and specialty pharmaceutical companies. It has products in approximately 140 countries and territories. The choice of this company as the research site is convenient as the researcher is employed at the pharmaceutical company. The

researcher thus has access to the PIs registered by the company in order to conduct the comparative textual analysis. The researcher also has access to the regulatory pharmacists that compiled the PIs in order to conduct focus group discussions about the sources of information used and the regulatory process involved in compiling generic medicine PIs. 2.3 Phases of data collection There were two phases of data collection. The first was the identification and collection of PIs. Four medicines registered by the pharmaceutical company were identified. This data set was used to compare specific categories of the originator medicine PIs with the corresponding categories of the generic medicine PIs. The data set obtained from the first phase of data collection was used to address the first objective of the study i.e. To describe the differences between originator medicine PIs and generic medicine PIs with respect to the listed indications, contraindications, warnings, interactions, dosage and directions for use, side-effects and special precautions. The second phase of data collection was empirical. A focus group discussion was held with six members of the regulatory team employed at the pharmaceutical company. The data set obtained from the second phase of the study was used to address the remaining two objectives of the study; the process that regulatory pharmacists follow for the compilation of a PI, the sources of information that they draw on, and their perceptions and experiences of compiling generic medicine PIs for approval by SAHPRA. The researcher has ensured trustworthiness of the qualitative research by employing the use of triangulation between the data sets obtained from the different methods used in the study. Triangulation involves the use of different methods which form the major data collection strategies for qualitative research (Shenton, 2004). Triangulation using different methods makes provision for the credibility of the research and also reduces investigator bias thereby making provision for confirmability of the research. 2.4 Data Sets 2.4.1 Package Inserts Four generic medicines, two hypotensives and two tranquilisers, registered and marketed by the pharmaceutical company were selected and the PIs for these medicines were compared to the corresponding originator brand medicine PI registered in South Africa. The PIs of the selected medicines were sourced fromthe pharmaceutical company's regulatory affairs folder. The inclusion criteria for the drug selection were as follows: a) The generic medicine is currently being marketed in South Africa. b) The generic medicine was registered by the company in the last 5 years. The drugs selected for inclusion in the study are shown in Table 1. Table 1 Selected generic equivalent versus corresponding originator brand, molecule name and pharmacological classification Originator brand Generic equivalent* Molecule Pharmacological classification Atacand® GENERIC CANDESARTAN Candesartan cilexitil Hypotensive Micardis® GENERIC TELMISARTAN Telmisartan Hypotensive Seroquel® GENERIC QUETIAPINE Quetiapine fumarate Tranquiliser Zyprexa® GENERIC OLANZAPINE Olanzapine Tranquiliser * The trade names of the generic equivalent have been changed. Two medicines classified as hypotensives, Candesartan cilexitil and Telmisartan, and two medicines classified as tranquilisers, Quetiapine fumarate and Olanzapine were selected for analysis. These classes of drugs are widely and commonly used in South Africa. Both these classes of medicines are used for the treatment of chronic conditions and contribute to the utilization of a large number of medicines in the South Africa market. Two divergent markets were compared i.e. Cardiovascular and Central Nervous System. Medicines with different pharmacological classifications were selected so that the research would be able to accommodate more than only one category of medicine registered at the company. The results obtained would then be an indication of medicines that were registered across the business and not only to a specific class of medicine. Specific categories within the PIs were selected for analyses. These are the listed indications, recommended dosage, special precautions, contraindications, side-effects, interactions and warnings. These categories were selected because these sections contain information that are regarded as the most important for the health care provider and the patient (Filby, 2008). 2.4.2 Focus group A focus group discussion was conducted with the regulatory staff of the company. Focus group discussion is a qualitative research method. This method allows an interviewer to ask study participants specific questions about a topic. This method is an appropriate choice for the research being conducted because it would provide the added dimension of interaction among study participants (Wong, 2008). Focus group discussions have been criticised for the vulnerability to bias. If there are dominant member/s in the group, it is advised that the interviewer should be aware of how the thoughts and ideas of these group members may influence the group. To deal with this criticism the researcher used the turn-taking approach. This approach ensured that each participant had a turn to contribute to the discussion. The focus group consisted of six participants employed at the company, viz. four registration pharmacists and two regulatory affairs officers. The pharmacists, including the regulatory affairs director, regulatory manager, and officers participating in the focus group, are all actively involved in the direct compilation of generic PIs. The participants and their qualifications are provided in Table 2. The regulatory staff have been employed at the pharmaceutical company for at least two years and have a lot of experience in the compilation of generic medicine PIs. Table 2 Participants of the focus group and their qualifications Name* Qualification No. of years employed in regulatory department Job title Lynn Bachelor of Pharmacy, Master of Science in Medicine (Pharmaceutical Affairs) 6 Regulatory Affairs Director and Responsible Pharmacist Carol Non-pharmaceutical 10 Regulatory Affairs Manager Bridget Bachelor of Pharmacy 3 Regulatory Affairs Pharmacist Miya Bachelor of Pharmacy, Master of Science in Medicine (Pharmaceutical Affairs) 5 Senior Regulatory Affairs Pharmacist and Responsible Pharmacist Tammy Bachelor of Pharmacy 2 Senior Regulatory Affairs Pharmacist Thea Qualified post basic pharmacist assistant 6 Senior Regulatory Affairs Officer * pseudonyms have been used. The focus group discussion focused on the following topics (see Appendix B): The results obtained in analysis of the comparison between the originator PI (OPI) and generic PI (GPI); the generic medicines registered by the company; the process followed to register a product, the sources of information used and the experiences the pharmacists had gained over time in the compilation of generic medicine PIs for approval by SAHPRA. The discussions were audio recorded and transcribed to facilitate data analysis. The focus group discussion was conducted in the boardroom at the pharmaceutical company. The venue was quiet, comfortable and convenient. The focus group participants sat ata table and were able to see and hear one another clearly. 2.5 Ethical considerations Approval to conduct the study was obtained from the Witwatersrand Human Research Ethics Committee prior to conducting this study (see Appendix C). The researcher obtained permission from the research site. Informed consent was obtained from all the participants of the study. 2.6 Data analysis 2.6.1 Package inserts A checklist was developed to record the differences in text noted in the selected categories of the generic medicine package and the originator medicine PI (see Appendix A). The following categories contained in the PI were compared and reviewed: - Indications - Contraindications - Warnings - Interactions - Dosage and directions for use - Side-effects - Special Precautions A manual comparative textual analysis was conducted on the differences that were noted on the checklist. 2.6.2 Focus group discussion The audio recorded focus group discussion was transcribed. A thematic content analysis was used to analyze the discussion. Thematic content analysis is a method of data analysis that is used to identify common themes that exist in the text (Burnard, Gill, Stewart, Treasure & Chadwick, 2008). The results of the textual comparisons were triangulated with the information obtained in the focus group interview. CHAPTER 3 RESULTS AND DISCUSSION A generic medicine is expected to provide the same therapeutic effect as the corresponding originator medicine (Dunne, Shannon, Dunne, & Cullen, 2013). Hence the information provided in an originator medicine PI and its corresponding generic medicine package is expected to be the same. The results of this study show that there are considerable differences between the information presented in the PIs. These differences stem from the sources of information that were used to compile the GPI and the regulatory challenges personnel face in obtaining approval of the GPI. In the context of this research the applicant is the pharmaceutical company that has applied to SAHPRA for registration of a generic medicine. 3.1 Comparative textual analysis of the OPI and GPI 3.1.1 Indications A comparison of the indications listed in the GPI and OPI of the four selected medicines revealed only one minor difference for one product, GENERIC OLANZAPINE. Table 3 shows that the phrase "in controlled trials" was removed from the indication however the indication for schizophrenia was still listed. The elimination of the words "in controlled trials" was discussed with participants of the focus group. Miya commented that, "the health authority evaluators always remove the reference to clinical trials". The participants of the focus group believe that the reason for removing the words clinical trials is because clinical trials are not conducted using generic medicines and hence it is incorrect to state this on the GPI even though it is stated on the OPI. The removal of clinical information by the regulatory staff and by the health authority evaluators is of major concern. Generic medicine manufacturers do not repeat the clinical studies that were performed by the originator company and the safety and efficacy profile of the generic medicine should mimic that of the originator medicine as the molecule contained in both medicines is exactly the same. Table 5, 6 and 9 show a similar pattern where clinical and non-clinical information was

removed in the PIs of GENERIC OLANZAPINE and GENERIC QUETIAPINE. Upon analysis of the generic PIs that were Page 16 of 73 evaluated, it is evident that the information on clinical and non-clinical trial information has been removed. Table 3 Core differences between the OPI and GPI noted under the heading of Indications Originator Brand Equivalent generic medicine No. of differences Atacand® GENERIC CANDESARTAN 0 Micardis® GENERIC TELMISARTAN 0 Seroquel® GENERIC QUETIAPINE 0 Zyprexa®: - The antipsychotic efficacy of Zyprexa® was established in controlled trials of schizophrenia in patients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech) GENERIC OLANZAPINE: - The antipsychotic efficacy of GENERIC OLANZAPINE was established in schizophrenia patients in the treatment ofpositive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech) 1 3.1.2 Contraindications A comparison of the contraindications listed in the GPI and OPI revealed significant differences. Table 4 shows that the GPIs include several important contraindications that have not been listed on the PIs. The GPIs were shown to be more of a comprehensive source of information when compared to the OPIs. Three out of the four medicines had listed additional contraindications in the GPI that were not listed in the OPI. GENERIC OLANZAPINE was the only medicine whose contraindications matched those in the OPI. For one medicine, GENERIC CANDESARTAN, hepatic impairment was not listed as a contraindication whereas it was stated as a contraindication on the OPI. Another finding in the hypotensive class of medicines was that the limit for creatinine clearance was stated to be different in the GPIs compared to that stated in the OPIs i.e. 15 ml/min vs 30 ml/min. The implication of these differences is that the OPI would be able to be used in cases where the GPI is contraindicated. The different limits for creatinine clearance would mean that patients who had a creatinine clearance of 15 ml/min would not be able to use the GPI for treatment. However, this should not be possible because the molecule contained in the GPI and the OPI is identical and should be contraindicated in the same group of patients. The findings were discussed in the focus group and participants noted that it is common for the GPI to have more contraindications as well as more warnings, special precautions, interactions and side-effects than those listed in the OPI. It was agreed among participants that it is common for the GPI to have different limits for creatinine clearance than the limit stated in the OPI. The reason for these differences is because during the process of compiling a GPI, the regulatory staff align the GPI with the latest safety data that is available globally. Tammy explained that it is the company's responsibility to ensure that the GPI provides patients and health care providers with latest safety information even if the OPI does not contain this information. Miya said that, "the company could be sued should the medicine be used in a group of patients where it is contraindicated and the GPI does not mention this as a contraindication". There are a few reasons for the OPI not containing the latest information available globally. It is suggested that the originator company has applied for inclusion of additional contraindications into the OPI and this is under review at the health authority. It is a consideration that the originator company has not applied for inclusion of additional contraindications and the OPI has not been updated after registration was obtained. Both scenarios are possible. The lengthy evaluation timelines by the health authority may be holding up the update to the OPI since the originator company will not be able to update the OPI unless health authority approval is obtained. On the other hand, the originator company may not have applied for inclusion of the additional contraindications as the health authority does not routinely review the PIs of registered medicines and would not force the originator company to update its PI in line with latest Page 18 of 73 safety information. Tammy explained that the latter is unlikely because the originator company is obligated to provide patients and health care providers with latest safety information. It is more likely that the originator company has applied for the inclusion of the additional information and has not obtained health authority approval as yet, hence the OPI is not as up to date as the GPI. These differences highlight a huge risk to patients and health care providers. Health care providers could prescribe the OPI for patients in which the medicine is contraindicated. This could result in patient fatalities. Table 4 Core differences between the OPI and GPI noted under the heading of Contraindications Originator Brand Equivalent generic medicine No. of differences noted Atacand®: - Very severely impaired renal function (creatinine clearance < 15 ml/min) - Severely impaired hepatic function GENERIC CANDESARTAN: - Very severely impaired renal function (creatinine clearance < 30 ml/min) - hepatic impairment was not listed in the GPI – A reduced dosage is recommended 7 Additional contraindications listed in the GPI: - Hereditary or idiopathic angioedema - Renal artery stenosis in patients with a single kidney - Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride - Porphyria - Lithium therapy: Concomitant administration may lead to toxic blood concentrations of lithium Originator Brand Equivalent generic medicine No. of differences noted Micardis®: - Severe renal impairment GENERIC TELMISARTAN: - Severe renal impairment (Creatinine clearance, 30 ml/min) 12 Additional contraindications listed in the GPI: - A history of angioedema related to previous therapy with Ace inhibitors or angiotensin receptor blockers (ARB's). Such patients must never be given these medicines. - Hereditary or idiopathic angioedema - Hypertrophic obstructive cardiomyopathy (HOCM) - Bilateral renal artery stenosis - Renal artery stenosis in patients with a single kidney - Aortic stenosis - Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride - Porphyria - Lithium therapy: Concomitant therapy with - Generic telmisartan may lead to toxic blood levels of lithium - Pregnancy and lactation Originator Brand Seroquel®: - Hypersensitivity to any of the components - Pregnancy and lactation, as safety has not been established Equivalent generic medicine GENERIC QUETIAPINE: - Hypersensitivity to any of the components - Pregnancy and lactation, as safety has not been established No. of differences noted 2 - Safety and efficacy in children and adolescents havenot been demonstrated - Advanced liver and renal function impairment, as safety has not been demonstrated - Safety and efficacy in children and adolescents have not been demonstrated - Advanced liver and renal function impairment, as safety has not been demonstrated Additional contraindications listed in the GPI: - Quetiapine is not indicated for use in elderly patients with dementia exhibiting behavioural disturbance - Co-administration with azole antifungals, macrolide antibiotics and HIV protease inhibitors Zyprexa® GENERIC OLANZAPINE 0 3.1.3 Warnings A comparison of the warnings listed in the GPI and OPI revealed that three out of the four medicines that were compared showed differences in the warnings that was provided. Table 5 shows that additional warnings were provided in the GPI for two of the medicines i.e. GENERIC CANDESARTAN and GENERIC QUETIAPINE. The Atacand® PI referred the patient to the specific section on pregnancy and lactation for warnings whereas the GPI PI stated the warning for pregnancy under the Warning heading. Thea said that, "this is not an uncommon finding and that the placement of the warning for pregnancy and lactation is dependent upon the health authority evaluator". Carol commented that "there is no clear guidance on whether it should be stated under the heading of warnings or under pregnancy in the PI". What stands out, is the lack in consistency as to where the information appears in the OPI versus where it appears in the GPI. Bridget said that, "it is ideal for patients to be able to refer to either PI and be able to locate the information in the same section rather than to have to find it under a different heading". Table 5 shows that the PI for GENERIC QUETIAPINE contained more warnings than that of the corresponding OPI. Again, it can be noted that the GPI is able to provide a more comprehensive list of warnings for the medicine. Tammy commented that "the additional warnings have been included in line with the latest originator medicine PI that was registered and approved overseas". The PI for GENERIC OLANZAPINE revealed that non-clinical data was removed in the GPI. Participants in the focus group explained that the removal of non-clinical data is requested by the SAHPRA evaluators because the registration of generic medicines do not require non-clinical studies to be submitted for evaluation and approval and that even though it is present in the OPI, it must be removed in the GPI. Non-clinical trials are performed to determine the pharmacokinetics, pharmacodynamics and safety profile of the drug. Non-clinical safety assessments are done by utilizing animal toxicological studies. The data from these studies are used to determine if there could be any potential safety risk when used in humans (TM, 2015). The information obtained during non - clinical trials determine the viability of progressing with further trials on the drug. Regulatory authorities across the world require non-clinical data prior to registration of an innovator medicine (Umscheid, Margolis, & Grossman, 2011). It is interesting to note that the originator company felt that this information was important enough to include into the OPI however this was removed in the GPI. The data obtained during non- clinical studies using originator drugs are applicable to generic medicines and should be included into the GPI. The registration of a generic medicine does not require clinical studies to be performed because they were already carried out using the originator medicine which contains the same active molecule. Hence the safety profile of the

originator medicine is applicable to that of the generic medicine. Page 22 of 73 Table 5 Core differences between the OPI and GPI noted under the heading of Warnings Originator Brand Equivalent generic medicine No. of differences noted Atacand®: - Refer to pregnancy and lactation for warnings GENERIC CANDESARTAN: Warning listed in the GPI: Should a woman become pregnant while receiving GENERIC CANDESARTAN, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine 1 Micardis® GENERIC TELMISARTAN 0 Seroquel® - Hyperglycaemia and diabetes mellitus: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. GENERIC QUETIAPINE: - Hyperglycaemia and diabetes mellitus: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including GENERIC QUETIAPINE. 4 - Patients with an established - Patients with an established diagnosis of diagnosis of diabetes mellitus who are diabetes mellitus who are started on atypical started on atypical antipsychotics such antipsychotics such as GENERIC as Seroquel, should be monitored QUETIAPINE, should be monitored regularly regularly for worsening of glucose for worsening of glucose control. control. - Patients with risk factors for diabetes - Patients with risk factors for diabetes mellitus who are starting on treatment mellitus who are starting on treatment with with atypical antipsychotics as atypical antipsychotics as GENERIC Seroquel, should be monitored for QUETIAPINE, should be monitored for symptoms of hyperglycaemia including symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and polydipsia, polyuria, polyphagia, and weakness. weakness. Originator Brand - Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as Seroquel, should undergo fasting blood glucose testing. - In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as Seroquel, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of suspect drug. Equivalent generic medicine - Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as GENERIC QUETIAPINE, should undergo fasting blood glucose testing. - In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as GENERIC QUETIAPINE, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of suspect drug. No. of differences noted Additional warnings listed in the GPI: - Where the use of GENERIC QUETIAPINE in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances, over sedation and complications associated with hyperglycaemia. Before prescribing GENERIC QUETIAPINE clinicians are advised to carefully assess the risks and benefits of the use of GENERIC QUETIAPINE in elderly patients with dementia as there has been an increase in the cerebrovascular events. In these cases, the risk prediction for stroke in the individual patient must be taken into account. Originator Brand Equivalent generic medicine - GENERIC QUETIAPINE must be used in caution in patients with known cardiovascular disease or other conditions predisposing to hypotension - GENERIC QUETIAPINE must be discontinued if signs and symptoms of tardive dyskinesia appear - GENERIC QUETIAPINE must be discontinued and appropriate medical treatment given in case of neuroleptic malignant syndrome No. of differences noted Zyprexa®: - Hyperprolactinaemia: Zyprexa® elevates prolactin levels and a modest elevation persists during chronic administration. An increase in mammary gland neoplasms has been found in rodents after chronic administration of antipsychotic medicines and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumours in rodents is unknown. GENERIC OLANZAPINE: - Hyperprolactinaemia: GENERIC OLANZAPINE elevates prolactin levels and a modest elevation persists during chronic administration. 1 3.1.4 Interactions A comparison of the interactions listed in the GPI and OPI revealed that all four medicines showed differences in the interactions that were listed. Miya explained that the global pharmacovigilance systems offer a platform for suspected interactions between medicines to be reported and investigated. The reporting of the suspected interactions happens after the registration of a medicine. The PI that is available globally would be updated in line with latest information that has been obtained from the global pharmacovigilance systems. This could be a reason why the interactions listed in the local OPI and the GPI are different. This difference could also be noted in the side-effects section of the PI. The WHO explains pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Pharmacovigilance has been expressed as a key component for effective drug regulation and has been cited as the worldwide master key for drug safety monitoring (Jeetu & Anusha, 2010). Miya commented that, "all generic companies have a pharmacovigilance department that record and investigate any adverse events that are reported by health care providers and patients". Often when an originator medicine becomes available on the market, only the interactions discovered during clinical trials are listed in the PI because these are the only known interactions that exist. When patients begin taking the medicine additional interactions are noted and can be picked by pharmacovigilance systems or post marketing studies. Miya thought that it was possible that the originator company may have applied for the local OPI to be updated but that, these changes may still be undergoing evaluation at the health authority level. Table 6 shows that the PI for GENERIC CANDESARTAN states the following, "Post marketing reports suggest a rare but significant interaction with increase of INR and bleeding with concomitant warfarin therapy ". This is an additional interaction between the concomitant use of warfarin and candesartan cilexitil. Although the OPI states that warfarin was investigated during clinical pharmacokinetic studies it does state that the concomitant use of these medicines leads to an increase in INR (International Normalised Ratio) and bleeding. This is a significant interaction and was listed in the GPI only. This data was derived from post marketing reports and included into the GPI by the regulatory affairs pharmacist that was compiling the GPI. Table 6 shows that an additional interaction listed for GENERIC TELMISARTAN was not listed in the OPI. The GPI stated that the concomitant treatment of telmisartan with non-steroidal anti-inflammatory drugs (NSAIDS) is associated with the potential for acute renal insufficiency in patients who are dehydrated and that patients receiving NSAIDS concomitantly with telmisartan need to be adequately hydrated. Health care providers who prescribe the OPI may not be aware of this interaction and could prescribe GENERIC CANDESARTAN for a patient who is not adequately hydrated and the patient would be at risk of developing renal problems. NSAIDs are very commonly used by patients and can be obtained as over the counter preparations at pharmacies. The PI for Seroquel® stated that the dose of Quetiapine would have to be reduced when taken with potent CYP34A inhibitors such as antifungals and macrolide antibiotics however the GPI stated that concomitant use of quetiapine and potent CYP34A inhibitors such as HIV protease inhibitors, azole antifungals and macrolide antibiotics were contraindicated. This finding is important because it illustrates that the GPI not only advises that the concomitant use of quetiapine and potent CYP34A inhibitors is contraindicated but it also provides more specific examples of CYP34A inhibitors. Human immunodeficiency virus (HIV) is very prevalent in South African and hence the inclusion of this information is vital. The GPI is also specific in noting the class of antifungals as azole antifungals whereas the OPI fails to do so. Again, the comparison of information between the OPI and GPI shows that the GPIs contained more comprehensive information. Table 6 shows the removal of statistical clinical trial information in the PI of GENERIC OLANZAPINE. The removal of clinical trial information was also noted in Table 1. Table 6 Core differences between the OPI and GPI noted under the heading of Interactions Originator Brand Equivalent generic medicine No. of differences noted Atacand®: - No interactions of clinical significance have been identified - Compounds which have been investigated in clinical pharmacokinetic GENERIC CANDESARTAN: - No interactions of clinical significance have been identified - Compounds which have been investigated in clinical pharmacokinetic 1 Originator Brand studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives, glibenclamide, nifedipine and enalapril - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with Atacand and careful monitoring of serum lithium levels is recommended during concomitant use. Equivalent generic medicine studies include hydrochlorothiazide, digoxin, oral contraceptives, glibenclamide and nifedipine and enalapril - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with GENERIC CANDESARTAN and careful monitoring of serum lithium levels is recommended during concomitant use. No. of differences noted - The antihypertensive effect of Atacand - The antihypertensive effect of Atacand may be enhanced by other may be enhanced by other antihypertensives. antihypertensives. - The bioavailability of candesartan is - The bioavailability of candesartan is not not affected by food. affected by food. Additional interaction listed in the GPI: Post marketing reports suggest a rare but significant interaction with increase of INR and bleeding with concomitant

warfarin therapy Micardis®: - May increase the hypotensive effect of other antihypertensive agents - Compounds which have been studied in pharmacokinetic trials include digoxin, warfarin, HCTZ, glibenclamide, paracetamol, ibuprofen, simvastatin and amlodipine - For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (in a single case a GENERIC TELMISARTAN: - May increase the hypotensive effect of other antihypertensive agents - Compounds which have been studied in pharmacokinetic trials include digoxin, warfarin, HCTZ, glibenclamide, paracetamol, ibuprofen, simvastatin and amlodipine - For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (in a single case a 1 Originator Brand Equivalent generic medicine No. of differences noted 39%), monitoring of plasma digoxin levels should be considered - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with Micardis. - Careful monitoring of serum lithium levels is recommended during concomitant use. 39%), monitoring of plasma digoxin levels should be considered - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with Micardis. - Careful monitoring of serum lithium levels is recommended during concomitant use. Additional interactions listed in the GPI: Concomitant treatment with NSAIDS (including aspirin at anti-inflammatory dosage regimens. COX-2 inhibitors and non-selective NSAIDS) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin- angiotensin-system, like GENERIC TELMISARTAN, may have synergistic effects. Patients receiving NSAIDs and GENERIC TELMISARTAN should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. A reduced effect of antihypertensive medicines, like GENERIC TELMISARTAN, by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDS Originator Brand Seroquel®: - In a multiple dose trial in healthy volunteers to assess the pharmacokinetics of Seroquel given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean Cmax and AUC of Seroquel of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half life of Seroquel increased from 2,6 to 6,8 hours, but the mean tmax was unchanged. Due to the potential for an interaction of similar magnitude in a clinical setting, the dosage of Seroquel should be reduced during concomitant use of Seroquel and potent CYP34A inhibitors (such as antifungals and macrolide antibiotics) Equivalent generic medicine GENERIC QUETIAPINE: - The co-administration of ketoconazole and GENERIC QUETIAPINE may result in a significant (5 -fold) increase in the AUC of GENERIC QUETIAPINE. On the basis of this, concomitant use of GENERIC QUETIAPINE and potent CYP34A inhibitors, such as HIV protease inhibitors, azole antifungals and macrolide antibiotics, is contraindicated. Additional interactions listed in the GPI: - GENERIC QUETIAPINE should be used in caution in patients also receiving antihypertensives or medicines that prolong the QT interval - GENERIC QUETIAPINE may antagonize the actions of dopaminergics, such as levodopa No. of differences noted 3 Zyprexa®: - In clinical trials with oral administration, olanzapine was not associated with a persistent increase in absolute QTC intervals. Only 8 of the 1685 subjects had increased QTc interval on multiple occasions. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients GENERIC OLANZAPINE: - As with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients when congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesemia. 1 Originator Brand Equivalent generic medicine No. of differences noted when congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesemia. 3.1 .5 Dosage and directions for use A comparison of the dosage and directions for use listed in the GPI and OPI revealed that only two medicines showed differences in the dosage and directions for use. Table 7 shows that GENERIC CANDESARTAN was contraindicated in patients with impaired renal function whereas the OPI advised using a lower dose of 4 mg. It is interesting to note that in Table 7 the OPI states that in patients with more severe renal impairment (i.e. creatinine clearance < 15 – 30 ml/min/1. 73 m2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be used however in Table 4 it lists severely impaired renal function as a contraindication. The normal corrected GFR is 80– 120 mL/min/1.73m2, impaired renal function is 30–80 mL/min/1.73m2 and renal failure is less than 30 mL/min/1.73m2 (Nankivell, 2001). The information provided in the OPI is not consistent within the different sections of the OPI. An additional statement was included into the dosage and directions for use of GENERIC OLANZAPINE. Tammy said that, "this data is included in line with latest safety data". The SAHPRA guidelines emphasize that the dosage and directions for use of the OPI and GPI should be the same. The WHO defines a generic medicine as a pharmaceutical product which is interchangeable with the originator brand product. Health care professionals will therefore prescribe and use the generic medicine in the same way as the originator product. Should the dosage and directions for use be different, this will have major consequences for treatment. A generic manufacturing company has the responsibility of ensuring that the information provided in the GPI is the same as that of the information provided in the PI of the originator medicine (Narang, 2016). The identical dosage and directions for use between the GPI and OPI would allow physicians to use the generic medicine with confidence. If the information provided under this section is different then it leads one to question whether the generic medicine is truly interchangeable with the originator brand product. As previously explained it is possible that the originator company may have applied for these changes to be made in the local OPI and these may still be under evaluation at the health authority. Table 7 Core differences between the OPI and GPI noted under the heading of Dosage and Directions for use Originator Brand Atacand®: - Use in impaired renal function: No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 ml/min/1. 73 m2 BSA). In patients with more severe renal impairment (i.e. creatinine clearance < 15 – 30 ml/min/1. 73 m2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be used. Equivalent generic medicine GENERIC CANDESARTAN: - Use in impaired renal function: No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 ml/min/1.73 m2 BSA). In patients with more severe renal impairment (i.e. creatinine clearance < 30 ml/min/1.73 m2 BSA), GENERIC CANDESARTAN is contraindicated. 1 No. of differences noted Micardis® GENERIC TELMISARTAN 0 Seroquel® GENERIC QUETIAPINE 0 Originator Brand Equivalent generic medicine No. of differences noted Zyprexa®: - Psychotic disorders: Zyprexa® tablets should be administered on a once a day schedule without regards to meals, generally beginning with an initial dose of 5 to 10 mg/day, with a target dose of 10 mg/day within several days GENERIC OLANZAPINE: - Psychotic disorders: GENERIC OLANZAPINE tablets should be administered on a once a day schedule without regards to meals, generally beginning with an initial dose of 5 to 10 mg/day, with a target dose of 10 mg/day within several days 1 - In order to evaluate efficacy and guard against side-effects, dosage increases should not be considered before one week, since steady state for olanzapine would not be achieved for approximately one week. The dose range is from 5 mg to 20 mg per day. Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment - In order to evaluate efficacy and guard against side-effects, dosage increases should not be considered before one week, since steady state for olanzapine would not be achieved for approximately one week. The dose range is from 5 mg to 20 mg per day. Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment - Acute mania in bipolar disorder: initial dose: Zyprexa® should be administered on a once a day schedule without regard to meals, generally beginning with 10 mg. Dosage adjustments within the dose range of 5 mg to 20 mg, if indicated, should not occur at intervals of not less than 24 hours. - Acute mania in bipolar disorder: initial dose: GENERIC OLANZAPINE should be administered on a once a day schedule without regard to meals, generally beginning with 10 mg. Dosage adjustments within the dose range of 5 mg to 20 mg, if indicated, should not occur at intervals of not less than 24 hours. - Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg per day. For patients who have been receiving Zyprexa® for - Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg per day. For patients who have been receiving GENERIC OLANZAPINE for Originator Brand Equivalent generic medicine No. of differences noted treatment of manic episode, continue therapy for preventing reoccurrence at the same dose. An increase to a greater dose than the recommended starting dose, within the range of 5 mg to 20 mg per day, is advised only after appropriate clinical assessment and should generally occur at intervals of not less than 24 hours. The safety of doses above 20 mg/day has not been evaluated in clinical trials. Gradual tapering of the dose should be considered when discontinuing

Zyprexa®. treatment of manic episode, continue therapy for preventing reoccurrence at the same dose. An increase to a greater dose than the recommended starting dose, within the range of 5 mg to 20 mg per day, is advised only after appropriate clinical assessment and should generally occur at intervals of not less than 24 hours. The safety of doses above 20 mg/day has not been evaluated in clinical trials. Gradual tapering of the dose should be considered when discontinuing GENERIC OLANZAPINE. Additional dosage and directions for use listed in the GPI: Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment. A 5 mg starting dose should be considered for patients with hepatic impairment and may also be considered for the elderly patient. The safety of doses above 20 mg/day has not been evaluated in clinical trials. Improvement in the patient's clinical condition may take several days to weeks. Patients should be closely monitored during this period. 3. 1.6 Side-effects A comparison of the side-effects listed in the GPI and OPI revealed that all four medicines showed differences in the side-effects that were listed. Many additional side- effects were included into the GPI. Miya said that, "this finding is expected and that pharmacovigilance systems contribute to the inclusion of the additional side-effects". The frequency of the side-effects is mentioned in all of the generic PIs where they may previously not have been mentioned in the OPI. The side-effect listed in the GPI would be classified under a different heading as compared to the heading in the OPI. Table 8 shows that in the PI of Atacand® angio-oedema was listed as a side effect under the heading skin and subcutaneous tissue disorders with no indication of frequency whereas it is listed on the GPI as an Immune system disorder as less frequent: Angioedema. Miya explained that this is not uncommon and that generic medicine PIs may reflect a frequency and heading that is listed in line with data in the overseas OPI. At the time of compiling a generic medicine PI the regulatory staff would use the latest available information from available reference sources to classify the heading and include the frequency of the side-effect. Tammy said that the, "additional side-effects present in the overseas OPI is also included at the same time". The comparison of the side-effects listed in Table 8 showed that the GPIs had a more extensive side-effect profile. The PI for GENERIC QUETIAPINE showed many differences to the OPI Zyprexa®. The body system category under which the side-effect was listed was very different to the OPI. There were many additional side effects listed under each of the headings. For example, in Table 8, the OPI Zyprexa® stated under the body system musculoskeletal, side-effect: rhabdomyolysis. In the GPI, this was stated under the body system musculoskeletal, connective tissue and bone disorders, side effect: less frequent: Extremity pain, join paint, back pain, rhabdomyolysis. Patients who may be switched from the originator medicine to the generic medicine might be hesitant to use the generic medicine as they may believe that generic medicine causes more side effects and is less safe than the originator medicine because it causes more side effects. Table 8 Core differences between the OPI and GPI noted under the heading of Side- effects Originator Brand Equivalent generic medicine No. of differences noted Atacand®: - Skin and subcutaneous tissue disorders: Angio-oedema, rash, uticaria, pruritic GENERIC CANDESARTAN: - Skin and subcutaneous tissue disorders: rash, uticaria, pruritic Additional side-effects listed in the GPI:- The most frequently reported adverse reactions were hyperkalaemia, hypotension and renal impairment. These events were more frequent in patients over 70 years of age, diabetics or subjects who received other medicinal products. 4 - Musculosketal, connective tissue and bone disorders: Back pain - Musculosketal, connective tissue and bone disorders: Less frequent: Back pain, Arthralgia and myalgia - Immune system disorders: Less frequent: Angioedema - Gastrointestinal disorders: Less frequent: Nausea Originator Brand Equivalent generic medicine No. of differences noted Micardis®: - Infections and infestations: Common: Urinary tract infections (UTI), upper respiratory tract infections. GENERIC TELMISARTAN: - Infections and infestations: Less frequent: UTI including cystitis, upper respiratory tract infection including pharyngitis and sinusitis, sepsis including fatal outcome 14 - Blood and the lymphatic systemic disorders: Rare: eosinophilia, thrombocytopenia - Blood and the lymphatic systemic disorders: Less frequent: eosinophilia, thrombocytopenia Less frequent: Anaemia and neutropenia - Nervous system disorders: Rare: faintness - Nervous system disorders: Less frequent: faintness, Somnolence, headache, dizziness, fatigue - Vascular disorders Rare: hypotension - Vascular disorders Rare: hypotension, orthostatic hypotension - Respiratory, thoracic and mediastinal disorders: - Respiratory, thoracic and mediastinal disorders: Less frequent: dyspnoea, cough, interstitial lung disease - Skin and subcutaneous tissue disorders: Common: eczema Uncommon: increased sweating Rare: erythema, pruritis, angio- oedema, urticaria - Skin and subcutaneous tissue disorders: Less frequent: eczema, increased sweating, erythema, pruritis, uticaria, drug eruption, toxic skin eruption, rash - Musculoskeletal, connective tissue and bone disorders: - Musculoskeletal, connective tissue and bone disorders: Originator Brand Common: arthralgia, myalgia, back pain, cramps in legs or leg pain Uncommon: tendinitis like symptoms Rare: weakness Equivalent generic medicine Less frequent: back pain, muscle spasms, myalgia, arthralgia, pain in extremity, tendon pain No. of differences noted - General disorders and administration site conditions: Common: chest pain, influenza-like symptoms Rare: lack of efficacy - General disorders and administration site conditions: Less frequent: chest pain, influenza-like symptoms, weakness Additional side-effects listed in GPI: - Anaphylactic reaction, hypersensitivity, angioedema - Abnormal hepatic function/liver disorder - Renal impairment, including acute renal failure - Sepsis: An increased incidence of sepsis has been reported with telmisartan compared with placebo Hypotension - Abnormal hepatic function/ liver disorder: Most cases of abdominal hepatic function/ liver disorder occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions - Interstitial lung disease: Cases of interstitial lung disease have been reported in temporal association with the intake of GENERIC TELMISARTAN Originator Brand Equivalent generic medicine No. of differences noted Seroquel®: - Nervous system disorders: Dizziness, somnolence, Syncope Seizures GENERIC QUETIAPINE: - Nervous system disorders: Frequent: Dizziness, somnolence, headache, anxiety, syncope, extrapyramidal symptoms Less frequent: Seizures, neuroleptic malignant syndrome, tardive dyskinesia. 10 - Blood and lymphatic system disorders: Leucopenia, Eosinophilia, Neutropenia - Blood and lymphatic system disorders: Frequent: Leucopenia Less frequent: Eosinophilia, Neutropenia, Thrombocytopenia Reported but frequency unknown: Agranulocytosis - General disorders and administration site conditions: Asthenia, peripheral oedema Neuroleptic malignant syndrome - General disorders and administration site conditions: Asthenia, peripheral oedema, withdrawal symptoms - Vascular disorders: Orthostatic hypotension - Vascular disorders: Frequent: Orthostatic hypotension Less frequent: Venous thromboembolism - Immune system disorders: Hypersensitivity (angioedema, anaphylaxis, uticaria/rash) - Immune system disorders: Hypersensitivity (angioedema, anaphylaxis, uticaria/rash), Steven-Johnson syndrome - Reproductive system and breast disorders: Priaprism - Reproductive system and breast disorders: Priaprism, galactorrhoea Originator Brand Equivalent generic medicine Additional side-effects listed in the GPI: - Metabolism and nutritional disorder: Less frequent: Hyperglycaemia, diabetes mellitus - Psychiatric disorders: Frequent: Abnormal dreams, nightmares - Hepatobiliary disorders: Less frequent: Jaundice, hepatitis - Eye disorders: Reported but frequency unknown: asymptomatic changes in the lens of the eye with long-term treatment, blurred vision No. of differences noted Zyprexa®: - Metabolic: Diabetic coma, Diabetic ketoacidosis, Hypercholesterolaemia, Hyperglycaemia, Hypertriglycericaemia Peripheral oedema GENERIC OLANZAPINE: - Metabolic and nutritional disorders: Frequent: Weight gain, increased appetite Less frequent: Diabetic coma, Diabetic ketoacidosis, Hyperglycaemia, Hypertriglycericaemia, development or exacerbation of diabetes 14 - Musculoskeletal: Rhabdomyolysis - Musculoskeletal, connective tissue and bone disorders: Less frequent: Extremity pain, joint pain, back pain, rhabdomyolysis - Urogenital system: Very rare: Priapism - Reproductive system and breast disorders: Frequency unknown: Priapism, menstrual syndrome Originator Brand Equivalent generic medicine No. of differences noted - Skin and appendages: Rare: Rash - Skin and subcutaneous disorders: Less frequent: photosensitivity disorders, Frequency unknown: rash, alopecia - Hematology Common: Eosinophilia - Blood and lymphatic system disorders: Frequent: Eosinophilia, leucopenia, thrombocytopenia, neutropenia - Respiratory system: Pneumonia - Respiratory, thoracic and mediastinal disorders: Frequent: Pneumonia Less frequent: rhinitis, cough, pharyngitis Additional side-effects listed in the GPI: - Psychiatric disorders: Less frequent: personality disorder, amnesia, anxiety, euphoria, hostility - Nervous system disorder: Frequent: headache, agitation, nervousness, myoclonus, extrapyramidal effects, dystonia Less frequent: dyskinesia, movement disorder, articulation impairment, hypertonia, neuroleptic malignant syndrome, tardive dyskinesia - Eye disorders: less frequent: Amblyopia, blepharitis, corneal lesion - Cardiac disorders: Less frequent: Chest pain, tachycardia, changes in ECG parameters, ventricular tachydysrhythmias - Vascular disorders: Frequent: hypotension, peripheral odema - Gastrointestinal disorders: Frequent: abdominal pain Originator Brand Equivalent generic medicine - General disorders and administration site conditions: Frequency unknown: Fever, intentional injury - Investigations: high

creatine phosphokinase, decreased erythrocyte count, hematocrit, haemoglobin, leucocyte count, lymphocytes, thrombocytes and platelets, increased MCHC, monocytes and eosinophils, decreased bicarbonate, calcium phosphorous, albumin and total protein, increased chloride, GGT and phosphorous No. of differences noted 3.1.7 Special precautions A comparison of the special precautions listed in the GPI and OPI revealed that all medicines showed differences in the special precautions that were listed. Table 9 shows that additional special precautions were listed in the GPI of GENERIC QUETIAPINE and GENERIC OLANZAPINE. Bridget said that, "the special precautions in the GPI are aligned to global safety data available in the overseas OPI that is used when compiling the local GPI". In the hypotensive group of medicines, the generic medicine was contraindicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy. The OPIs had listed this as a special precaution and not as a contraindication. Another significant finding for GENERIC TELMISARTAN was that concomitant use of potassium sparing diuretics and GENERIC TELMISARTAN was not recommended whereas the OPI advised that potassium sparing diuretics should be used in caution with the originator medicine. This conflicting information means that the originator medicine could be used cautiously whilst the generic medicine is contraindicated. This should not be possible because the molecule contained in both the generic and originator medicine is the same and the information provided in the OPI and GPI should be identical. It is well known that generic medicines contain the same active pharmaceutical ingredient (API) as that of the corresponding originator medicine. The API is responsible for having the desired biological effect (Gavura, 2012). This means that the since the active ingredient is the same in both the originator and generic medicines, both medicines should behave in the same way and result in the same desired effect. The inconsistency in the provision of information compromises health care providers and patients. Table 9 shows that withdrawal information was included into the PI of GENERIC QUETIAPINE. This information is useful when patients no longer require treatment. The OPI fails to provide such information. The medicine should be gradually withdrawn otherwise the patient could experience withdrawal symptoms. The OPI for olanzapine stated that blood pressure should be periodically measured in patients over 65 years of age because postural hypotension was infrequently observed during clinical trials. Table 9 shows that this information was removed in the GPI. Non- clinical information on carcinogens, mutagenesis and fertility was also removed in the GPI. The participants of the focus group explained that the removal of non-clinical information was requested by the health authority evaluator as the clinical trial was not conducted using the generic medicine. Generic medicine applications piggy back on the studies that were performed by originator companies and hence do not have to perform their own clinical studies (Dunne, Shannon, Dunne, & Cullen, 2013). For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product (Hari Das, Prasant, Steffi, & Naushad, 2013). Bioequivalence testing links the generic medicine to the clinical studies that were conducted by the originator drug. The clinical studies performed on originator hence become applicable to the generic medicine as well and should be included in the GPI. Non-clinical trials are performed to determine the pharmacokinetics, pharmacodynamics and safety profile of Page 43 of 73 the drug. Non-clinical safety assessments are done by utilizing animal toxicological studies. The data from these studies are used to determine if there could be any potential safety risk when used in humans (TM, 2015). The data obtained during non- clinical studies using originator drugs are applicable to generic medicines and should be included into the GPI. Additional Information on plasma clearance in smokers and on lipids alterations was provided in the GPI. The removal of some information and addition of other information in the GPI showed a lack in consistency between the information presented in the GPI and the OPI. The special precautions listed for sorbitol, lactose and soya lecithin is important for patients who have an intolerance towards these excipients. The excipients contained in generic medicines may differ to those that have been used to manufacture originator medicines. This would explain why the special precaution does not appear on both the OPI and GPI. The excipients contained in the originator medicine has not been listed on the OPI and hence it is not known whether the originator medicine contains soya lecithin or lactose. The current SAHPRA guidelines state that the excipients contained in medicines must be listed on the PI. The fact that the excipients were not listed on the local OPI indicates that it had not been updated in line with current SAHPRA guidelines. Table 9 Core differences between the OPI and GPI noted under the heading of Special Precautions Originator Brand Atacand®: - Aortic and mitral valve stenosis: Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy Equivalent generic medicine GENERIC CANDESARTAN: - GENERIC CANDESARTAN is contraindicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy Total no. of differences noted 1 Originator Brand Micardis®: - Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy. Equivalent generic medicine GENERIC TELMISARTAN: - GENERIC TELMISARTAN is contraindicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy. Total no. of differences noted 3 - Hyperkalaemia: During treatment with other medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of other medicinal products that affect the renin- angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co- administered cautiously with Micardis - Based on experience with the use of other medicinal products that affect the renin- angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore not be co- administered with GENERIC TELMISARTAN - Sorbitol: Micardis tablets contains sorbitol and is therefore unsuitable for patients with hereditary fructose intolerance - Sorbitol special precaution was not listed in the GPI Originator Brand Seroquel®: - In clinical trials Seroquel was not associated with a persistent increase in QTc intervals. However, caution should be exercised when Seroquel is prescribed with drugs known to prolong QTc interval, especially in the elderly. Equivalent generic medicine GENERIC QUETIAPINE: Caution should be exercised when GENERIC QUETIAPINE is prescribed with drugs known to prolong QTc interval, especially in the elderly. Total no. of differences noted 2 - Effect on ability to drive and use machines: Seroquel may cause somnolence which may interfere with activities requiring mental alertness. Patients should be advised not to operate hazardous machines, or drive vehicles, until individual susceptibility is known. - Effect on ability to drive and use machines: GENERIC QUETIAPINE may cause somnolence which may interfere with activities requiring mental alertness. Patients should be advised not to operate hazardous machines, or drive vehicles, until individual susceptibility is known. Withdrawal recommendation: It is recommended that GENERIC QUETIAPINE be gradually withdrawn because of the risk of withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses with abrupt cessation. Recurrence of psychotic symptoms may also occur and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesis) have been reported. Additional special precaution listed in the GPI: - Lactose: GENERIC QUETIAPINE contains lactose. Patients with hereditary galactose intolerance, the Lapp lactase deficiency or glucose-galactose Originator Brand Equivalent generic medicine malabsorption should not take GENERIC QUETIAPINE Total no. of differences noted Zyprexa®: - Geriatric use: In clinical studies, in general, there was no indication of any different tolerability of Zyprexa® in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to Zyprexa®, should lead to consideration of a lower starting dose. As postural hypotension was infrequently observed in the elderly in clinical trials, it is recommended that blood pressure is measures periodically in patients over 65 years. GENERIC OLANZAPINE: - Geriatric use: In clinical studies, in general, there was no indication of any different tolerability of GENERIC OLANZAPINE in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to GENERIC OLANZAPINE, should lead to consideration of a lower starting dose. 7 - Orthostatic hypotension: Zyprexa® may induce orthostatic hypotension associated dizziness, tachycardia and in patients, syncope, especially during initial treatment period. - Orthostatic hypotension: GENERIC OLANZAPINE may induce orthostatic hypotension associated dizziness, tachycardia and in patients, syncope, especially during initial treatment period. Plasma clearance of olanzapine is higher in smokers. The combined effects of age, smoking and gender could lead to substantial

pharmacokinetic differences. The clearance in young smoking males, for example, may be 3 times higher than that in elderly non-smoking females. Dosing modification may be necessary in patients who exhibit a combination of Originator Brand Equivalent generic medicine factors that may result in slower metabolism of olanzapine Total no. of differences noted - Haematology: Caution should be exercised when using olanzapine in the following types of patients: - Low leucocyte and/or neutrophil counts due to any reason - History of medicine induced bone marrow depression/toxicity - bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy - Hypereosinophilic conditions or with myeloproliferative disease Thirty-two patients with clozapine- related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts. - Haematology: Caution should be exercised when using olanzapine in the following types of patients: - Low leucocyte and/or neutrophil counts due to any reason - History of medicine induced bone marrow depression/toxicity - bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy - Hypereosinophilic conditions or with myeloproliferative disease - Carcinogens: Based on the results of studies in mice and rats it was concluded that olanzapine is not carcinogenic. - Mutagenesis: Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and in vitro and in vivo mammalian tests. - Information on carcinogens removed from the GPI - Information on mutagenesis removed from the GPI Originator Brand Equivalent generic medicine Total no. of differences noted - Impairment of fertility: In rats, male mating, but not fertility, was impaired. Discontinuation of olanzapine treatment reversed the effect on mating performance. In female rats, oestrus cycles and reproduction parameters were influenced at doses higher than the maximum human dose. - Information on fertility removed from the GPI Additional special precautions listed in the GPI: - Lipid alterations: Undesirable alterations in lipids have been observed in patients with low leucocyte and/or neutrophil counts due to any reason, patients with a history of medicine-induced bone marrow depression/toxicity, patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy, and in patients with hypereosinophilic conditions or with myeloproliferative disease - Lactose: GENERIC OLANZAPINE tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take GENERIC OLANZAPINE. - Lecithin soya: GENERIC OLANZAPINE tablets contain lecithin soya. Patients who are allergic to peanut or soya, should not take GENERIC OLANZAPINE. 3.2 Summary of the textual analysis (First data set) The comparisons between the OPIs and GPIs showed that there are differences in the information that is provided under the various headings that were analysed in the package inserts. The key findings have been summarised below. The OPI and its corresponding GPI are not consistent in the information that it provides to the health care providers and to patients. Research conducted internationally indicates that this finding is not unique and that there is a lot of variability in the important information across all the investigated markets (Pfistermeister, et al., 2013). The listed contraindications, warnings, interactions, side-effects and precautions are more comprehensively provided for in the GPI. The GPI was able to provide important latest information that was not present in the OPI. The additional information provided in the GPI resulted in a PI that was of improved quality when compared to the OPI. However, if a patient or health care provider had to compare the information provided in the GPI and OPI it would appear different. The removal of clinical and non-clinical information as requested by the health authority evaluators and the additional information presented in the GPI could make it seem that the generic medicine is not as safe because it lists more contraindications and has more warnings, side-effects and special precautions than the OPI. The removal of non-clinical data from the GPI is of concern as the registration of generic medicines is based on the clinical and non-clinical studies that have been carried out using the originator medicine. A generic medicine is manufactured with the intention of being an alternative more cost-effective option for therapy but the differences noted between the OPIs and GPIs makes one question whether it really is equivalent to the originator medicines. This may affect physician and patient confidence with the use of generic medicines. 3.3 Sources of information used to compile a GPI SAHPRA guidelines do provide a list of reference sources that could be used for the compilation of a GPI. Discussions during the focus group generated additional sources of information that regulatory staff use to compile a GPI. Table 10 shows the reference sources listed by SAHPRA compared to the list of reference sources provided by the participants of the focus group. Table 10 Reference sources used for compilation of a GPI – SAHPRA recommended sources vs actual reference sources used SAHPRA recommended reference sources Actual reference sources used ? Most recently approved innovator PI ? Most recently approved originator PI available in the local commercial pack ? Reference books: - Good & Gilman - Martindale - USP dispensing information ? ? Reference books: - Good & Gilman - Martindale - USP dispensing information Company core data sheet is only ? Company core data sheet is only considered if substantiated by relevant data on which it is based ? considered if substantiated by relevant data on which it is based Other references or peer reviewed ? Other references or peer reviewed updated references, including information obtained from other regulatory authorities with which the Council aligns itself ? updated references, including information obtained from other regulatory authorities with which the Council aligns itself SAHPRA monographs ? ? SAHPRA monographs SAHPRA guidelines1 ? ? SAHPRA guidelines Most recently approved originator PI available overseas 1 SAHPRA guidelines for PIs comprise of the following guidelines: PIs for Human Medicines, 2014 Labelling of medicines containing sugars, 2015 Patient Information Leaflets, 2014 PIs for Human Medicines Standardised Texts, 2015 ? Most recently approved PI for the same medicine that is being applied for, that has already received approval by overseas regulatory authorities ? Latest edition of the Summary of product characteristics (SmPC), mainly the United Kingdom version As per the SAHPRA guidelines, pharmaceutical companies are required to use the most recent approved originator PI (PI) as the reference for the compilation of a generic PI. The guidelines state that the indications, dosage and directions for use and the safety profile for a generic medicine should at least be in line with that of the originator PI. The guideline also states that SAHPRA retains the discretion to require more or less details under the respective headings of the PI. SAHPRA guidelines recommend that applicants use the reference book Goodman & Gilman, to include additional information relating to pharmacological action. The Martindale is used for additional information relating to safety information. Other supplementary reference sources may be used i.e. USP Dispensing information, SAHPRA monographs and peer reviews references. Carol explained that SAHPRA guidelines are used primarily for structure and layout of the GPI. The guidelines are also useful when standardised texts for a specific condition or class of medicine is required or for when the sugar content of the medicine needs to be included. Other than for the reasons stated above, the OPI that is available in the local commercial pack is the primary reference source that is used to compile the GPI. Carol emphasized that the approved OPI that is registered overseas and/or the UK Summary of Product Characteristics (SmPC) are used for compilation when the local originator PI is outdated and does not contain the most recent available safety data. The SmPC is obtained electronically via the electronic medicines compendium (eMC) website and the document contains up to date, approved and regulated prescribing and patient information for licensed medicines. All the participants of the focus group agreed that the information under the headings contraindications, side-effects, warnings and special precautions of the GPI are updated in line with the overseas OPI and/or the UK SmPC. A significant finding is that the regulatory staff align the GPI to the latest information that is available internationally. The reason for the alignment with international information is because the local OPI is outdated. The company has its own set of global standards which has to ensure that the patient is protected from receiving outdated information, that the company is protected from reputational damage and that there is consistency in the labelling information in all products that are marketed internationally. The company is at a risk of being sued should important information be left out of the GPI. 3.4 Processes followed in the compilation of a GPI 3.4.1 Health authority process The health authority has not published a process for the compilation of a GPI. Guidelines have been published that provide information on the structure and content of the PI, however, the actual process has not been documented. Further to this there are no timelines allocated to the evaluation process. Once a GPI has been submitted for evaluation, there is no information provided as to when the pharmaceutical company can expect an outcome. Carol said that "it could around 4 years to receive the first clinical committee recommendation". 3.4.2 Internal process The focus group discussion revealed that there is agreement among the pharmacists about the process that is followed to compile GPIs. The process can be summarised into eight steps, refer Figure 1. Carol confirmed that the internal process that is described below has been developed by the regulatory staff through experience. Step 1 Obtain OPI Obtain the latest originator PI from the South African commercial pack. Step 2 Retype OPI Retype the originator PI into a word document. Step 3 Replace Trade Name Replace the trade name of the originator

medicine with the trade name of the generic medicine. Step 4 Amend in line with dossier information Amend the excipients, identification, presentation of the commercial pack and storage conditions so as to be in line with the information available in the generic medicine dossier Remove or reword information regarding the clinical studies conducted by the originator company depending on the content. Step 5 Check against latest reference sources Check this version of the GPI against the approved overseas OPI, UK SmPC and recommended reference books. Include any additional information. Step 6 Check indications Check the indications to ensure that there is no local patent protection on any specific indication. Remove any indication where a patent still exists. Step 7 Submit for review Submit the GPI as part of the dossier for approval by SAHPRA Step 8 Recieve CCRs and respond until GPI is approved Receive a Clinical Committee Recommendation (CCR) once the GPI has been evaluated by the clinical unit of SAHPRA. The CCR contains the evaluators' comments and suggestions after evaluating the GPI. Respond to and correct the GPI in line with the committee's comments. Resubmit the GPI for a second evaluation. Subsequent CCRs may be received until the GPI is approved by the clinical committee. Figure 1 Eight steps of GPI compilation 3.4.3 Amendment process The PI of registered medicines can only be changed or amended upon approval from SAHPRA. SAHPRA has provided an amendments guideline that allows for amendments to be done on registered medicines, however, there is no guidance on timelines for approval. Carol said that, "it could take around 1 ½ years for the applicant to receive any outcome". Bridget commented that "there is no process for regulatory staff to contact SAHPRA to find out if there is an outstanding amendment on a medicine". This provides a possible explanation as to why the local OPIs that were used in the textual analysis did not contain all the latest safety information that the GPI contained. It is possible the originator company has applied for an amendment to the OPI, however, they have not received any outcome from the health authority and hence are unable to update their PI. 3.5 Experiences and perceptions of regulatory affairs personnel 3.5.1 Accessibility of the local OPI During the focus group discussion, the participants explained that whilst the most recent local originator PI is the primary reference to be used for the compilation of a generic medicine PI, it is very difficult to obtain the most recent version. Often the PI that is available in the commercial pack of the originator medicine in South Africa is outdated and not in line with the corresponding overseas originator PI or UK SmPC. Bridget said that, "the compiler will include the latest updated information from the overseas originator PI and/or the UK SmPC into the GPI in order to ensure that the generic medicine PI contains the latest information". The latest safety information from acceptable reference books will also be included to ensure that the GPI contains the most updated information available at the time. This is often the reason why differences arise in the information presented in the OPI and the GPI. This is also the main reason why the side effect profile, warnings and special precautions of the generic medicine is more extensive than that of the local originator medicine. In the European Union (EU) and the United States (US), it is a requirement for originator companies to update their PIs in line with phase IV clinical trial data, pharmacovigilance data and ongoing research (Filby, 2007). It is therefore also possible that an amendment may have been submitted by the originator company, to SAHPRA to update the information that is available in the local OPI available in the commercial pack. Miya said that, "due to long timelines for review by SAHPRA the amendment may not be reviewed for many years and hence the originator medicine PI available in South Africa will not be in line with the latest information that is available globally". The generic pharmaceutical company will also not have oversight of the pending amendment on the OPI as there is no system in place to gain access to this information. 3.5.2 Administrative issues One of the issues that emerged from the focus group was the room for error in the procedure because the local OPI is retyped into a word document. Thea said that, "there is a possibility for errors to be made and for information to be missed out or repeated". Thea and Lynn said that, "due to time constraints, the word document may not be peer reviewed and hence the error will be submitted in the final version of the GPI". SAHPRA evaluators may not pick up this error during evaluation and this will lead to the information that is present in the OPI being different to that presented in the GPI. Thea, Bridget and Tammy said that, "they experience a lot of frustration in retyping an OPI into a word version for editing". Longer complex medicine PI e.g. antiretroviral medicines (a combination of multiple active ingredients) PIs are at greater risk due to the amount of information that needs to be retyped. Thea described the process as time consuming and exhausting. 3.5.3 Patent issues Another issue that was raised by Carol was around patent issues which SAHPRA does not concern itself with. Bridget said that, "it is the responsibility of the company to ensure that the patent issues are checked prior to product launch". Currently regulatory staff at the company remove indications due to an existing patent. This is a patent protection strategy that originator companies use to ensure market exclusivity. Hence the approved GPI may not contain some of the indications present in the OPI due to patent protection. Due to the long timelines for review, the regulatory staff find that once the GPI is approved, the patent on the indication has already expired and an application to include the indication on the GPI then needs to be submitted to SAHPRA for approval. This means that the product would be launched without the indication being listed on the GPI and only once approval has been obtained from SAHPRA can the indication be added into the GPI. Carol explained that as per the company's global policy all indications should be applied for at once and then prior to launch the applicant should remove those indications that have patents and only include them onto the PI once the patent has expired. The process of removing patented indications is internally referred to as "Carving". If SAHPRA were to implement this system it would prevent another application having to be submitted in order to add a new indication. This would lead to a decreased workload on the side of the health authority and on the regulatory staff of the company. It would also allow for the generic medicine to be used for an additional indication as soon as patent expiry without having to wait for approval from the health authority. 3.5.4 Challenges in dealing with the health authority All the regulatory staff described the process of compiling and submitting a GPI for approval by SAHPRA as frustrating and inconsistent. Lynn felt strongly that the system lacks transparency, reproducibility and overall integrity. 3.5.4.1 Quality of the Clinical Committee Recommendation (CCR) The group noted that clinical committee recommendations received from the evaluators are often inconsistent. Bridget, Tammy and Thea said that, "the information that has been requested for inclusion in the first CCR received from evaluators is asked to be removed in the second CCR". There is no reason or justification given for the removal. This leads to a lot of frustration as the staff member compiling the PI does not know why the evaluator is requesting the removal. Lynn said that, "a possible reason for this is that the PI is not reviewed by the same evaluator each time and hence each evaluator will have a different opinion on whether the information should be present or not". The level of training and skill set of the evaluators are not known. The applicant has to comply with the recommendations of the evaluators or face a further delay in approval. Lynn said that, "the allocation of a specific product to a specific team of evaluators rather than to any available evaluator would reduce the number of inconsistencies received in CCR". Carol said that, "It very unusual for a product to only receive one clinical recommendation". The product will most likely receive a second or third recommendation for information to be included or excluded or amended. This contributes to a very long delay in the approval of a GPI. Most times the second or third recommendations focus on spelling or the inclusion of a comma or a full stop. The focus of the evaluation shifts from actual medical content to finding spelling and grammar errors. All the participants of the focus group agreed that delaying a product's approval because of a full stop, comma or spelling mistake is extremely frustrating as the applicant could wait a further 3 – 6 months in order to gain clinical approval. Tammy said that, "at times, clinical committee recommendations request the applicant to justify statements that were taken directly from the OPI. It is possible that the OPI may not have been updated to the latest information available but the information was included since it is presented in the commercially available OPI. Thea explained that there are situations were recommendations received from the pharmaceutical and analytical unit mimic that received from the clinical unit. This results in a duplication of work. Communication between the different units of the health authority would prevent this from occurring and would also save time and resource for the health authority and the applicant. Lynn said that, "the GPIs are also manually assessed and the evaluators comments are written in pen on a hard copy of the GPI". The annotated GPI is then sent to the applicant. At times, staff members are unable to decipher what has been written on the GPI or what needs to be corrected. The comments are vague and the staff member compiling the response is left to interpret what he or she thinks is correct and respond accordingly. Should the regulatory staff misinterpret what is required then an additional CCR would follow leading to a further delay in approval. 3.5.4.2 Communication and transparency Carol said that, "there is no opportunity for a regulatory staff member to contact or approach the evaluator". The staff members explained that when they try to call or email SAHPRA they are often unsuccessful. If somebody does answer the phone, they are at most times unable to assist or hesitant to assist. Lynn

said that, "it is not possible to know the names of the evaluators or to speak or contact them directly. The process is not transparent and it is difficult to follow up on the approval of products or even to determine product status". Foreign regulatory authorities employ the use of more transparent review systems. As discussed in the literature review, both the TGA and the EMA provide public assessment reports upon review completion. The timelines for assessment by the EMA are clearly defined. Applicants are allowed to contact the evaluator during the approval process. A meeting or telephone call is arranged to discuss any queries. The above issues ultimately highlight the impact that the evaluator has on the overall approval process. Lynn said that, "if evaluators were accessible this would allow applicants to contact them directly and set up meetings or telephone calls to discuss Page 59 of 73 questions raised by the applicant". This would favour approval timelines instead of receiving numerous CCRs and would also lead to decreased work load for the applicant and the health authority. Tammy and Bridget said, "that there have been cases where the responses to clinical recommendations have been mislaid". They had received no communication from the health authority that the response has been mislaid. This was discovered when they had contacted the health authority via telephone in order to obtain a product status. No subsequent written communication was received. Thea and Bridget had to resubmit the response and this contributed to a further delay in obtaining approval. The health authority did not fast track this response and it waited in the queue for assessment. 3.5.4.3 Amendments Lynn said that, "the amendments of currently approved PIs also take a very long time for approval". Companies may need to do multiple updates to PIs and find themselves in a situation where the last amendment was not as yet approved and they already have to submit a new amendment. This causes a lot of confusion and results in the GPI that is present in the commercial pack being outdated and not in line with the foreign GPI available in overseas countries for the same product. This poses a risk as patients in South Africa do not have access to latest available medicine information. 3.5.4.4 Clinical committee meeting dates Currently clinical committee meetings are held at set dates that are determined by the health authority. This results in outcomes for multiple products being received at the same time. Lynn said that, "it would be useful if products could be discussed sooner rather than waiting for a clinical meeting date". This would allow applicants to receive recommendations as soon as they become available from evaluators. This would ultimately shorten the timelines for approval. Carol said that, "the current system needs to be revised". 3.5.4.5 Health authority backlog The health authority has acknowledged that a backlog exists and that the evaluation of products have been delayed. This is attributed to a lack of skilled staff and also due to a lack of service level agreements between the external evaluators reviewing the PIs and the health authority. Lynn said that, "the lack of proper evaluation and review systems coupled with human resource challenges contribute to the current backlog and hence the review process takes a long time to complete". 3.6 Summary of the focus group discussions (Second Data Set) The focus group discussion was conducted with regulatory affairs personnel who identified the sources of information that are used to compile the GPI. SAHPRA have recommended a list of sources that must be used to compile a GPI, however, the regulatory affairs personnel use additional sources of information to compile the GPI. The inclusion of additional information from additional sources results in a difference in the information that is provided in the GPI. The information that is included into the GPI is in line with the latest overseas OPI and/or the UK SmPC. The regulatory staff have had to use these additional resources for information as the primary source as recommended by SAHPRA, the local OPI, is considered outdated due to the omission of the latest product information available in the overseas OPI and UK SmPC. These findings are noted in the OPI for Atacand® in which the date of PI publication is listed as 30 November 2007. This date indicates that the OPI was last updated approximately 10 years ago. The regulatory affairs personnel identified the process that was used for the compilation of a GPI. The process used was described in eight steps. Currently SAHPRA have not recommended a process for the compilation of a GPI. The regulatory personnel have formulated these steps through their years of experience in compiling GPIs. Since SAHPRA have not recommended a process, the staff had to formulate their own process in order to ensure consistency of GPI compilations within the pharmaceutical company. The timeline for evaluation of a GPI and subsequent receipt of a clinical committee recommendation by the applicant is unknown. The process of amending a PI that has already gained SAHPRA approval is challenging and there are no clear timelines on how long this process can take. This could be a reason that explains why the local OPIs have been not been updated. The experiences and perceptions of the regulatory affairs personnel in compiling a GPI for approval by SAHPRA was explored. The regulatory staff have had many challenges in compiling the GPI, including accessibility to the latest local OPI. Due to the local OPI being outdated staff had to seek other sources of information to ensure that the GPI contained the most up to date information that is available globally. The staff also faced administrative issues. Manual typing up of the local OPI creates room for errors in the GPI. Applications to include additional indications into an approved GPI took long and resulted in an additional workload for both the applicant and the health authority. Another enormous challenge for the regulatory staff was the communication with the health authority. A GPI must undergo evaluation by the evaluators of the health authority prior to approval. The evaluators assess the GPI and determine which information should be deleted, added or amended. The review process is a contributor to the differences that were noted in the textual comparisons. The regulatory staff experience very poor levels of communication with the health authority. They are unable to contact the evaluators and even experience challenges in obtaining a product status via phone or email. There is no online system available to track or view the progress of a GPI that has been submitted for approval. The system lacks traceability and transparency. CHAPTER 4 CONCLUSIONS AND RECOMMENDATIONS The study evaluated the differences noted between the information presented in the originator medicine PI and the generic medicine PI. This comparative analysis of the PIs was manually performed using checklists. A focus group discussion was conducted with regulatory staff participants, involved in the compilation of generic medicine PIs, from one pharmaceutical company. The participants are involved in the compilation of generic medicine PIs. The differences noted in the textual analysis was discussed in the focus group. The sources of information that are used and the regulatory process that is followed for the compilation of a generic medicine PI was identified. The study explored the experiences and perceptions of the regulatory staff with regard to compiling a generic medicine PI for approval by the South African Health Product Authority. 4.1 Summary of findings As mandated by SAHPRA, the contents of a generic medicine PI (GPI) should be the same as that presented in the originator medicine PI because its compilation is based on the information present in the OPI. The results of the comparative textual analysis showed that this is not the case. The analysis showed that there was a large number of differences between the information presented in generic and originator medicine PIs. The GPI contained additional information under the various headings of the PI i.e. Contraindications, warnings, interactions, side-effects and special precautions. The additional information presented in the GPI was included by regulatory pharmacists who were responsible for the compilation of the GPI. The information was obtained from the latest information that was available in the list of reference sources used by the regulatory affairs staff (refer Table 10). The information that was included into the GPI was important to both the health care provider and the patient. The inclusion of additional latest information into the GPI resulted in it being a more comprehensive and accurate source of information than the OPI. Although the GPI was shown to contain vital information that the OPI lacked, it does eventually result in different information being provided in PI sources that are expected to be the same. The exclusion of clinical and non-clinical data accompanied with the comprehensive side- effect profile, additional contraindications, warnings, interactions and special precautions may lead one to believe that the generic medicine is not the same as the originator medicine even though the molecule contained in originator and the registered generic medicine is the same. It could also be perceived that the generic medicine is less safe because it has more side effects and more contraindications, warnings, interactions and special precautions. Patients may also believe that this is the reason why generic medicine is available at a cheaper price. It is therefore ironic that the increased quality of the GPI may undermine patient confidence when deciding to use generic medicines. The study found that the differences noted in the OPI and GPI could be attributed to the sources of information used to compile the GPI and the health authority review process. SAHPRA recommended that the latest locally available OPI be used as the primary source for compilation of the GPI, however, this is not what happens in practise. The local OPI is outdated and regulatory staff are then forced to seek alternative sources of information to ensure that the GPI contains the latest information that is available. Generic companies have to adhere to their own set of internal global standards and also need to ensure that they are not sued by patients should the information in the GPI be incorrect or inadequate. SAHPRA have not recommended a process for the compilation of a GPI or the amendment of an already registered GPI. Regulatory pharmacists

draw on their regulatory experiences and decide on the best way of GPI compilation. The local health authority process is flawed and does not support the timeous registration and access to generic medicine. There are no confirmed timelines for the approval of a generic medicine PI or an amendment to an already registered GPI. The regulatory process for compilation and approval of a GPI is unclear. The manual assessment of the GPIs by the health authority evaluators as well as a lack in the standardisation of recommendations received results in many reviews of the GPI prior to approval being obtained. The lack of an electronic tracking tool makes it difficult to track and trace the status of a GPI. Communication channels with the staff of the health authority are limited and the interaction is often very poor. The lack of timelines and a Page 64 of 73 structured, transparent system for generic medicine review contributes to a delay in registration and ultimately a delay in access to generic medicine. 4.2 Recommendations The regulatory staff at the pharmaceutical company describe the process of compilation and approval of a GPI as inconsistent and frustrating. The following recommendations are proposed: ? The current SAHPRA system lacks transparency. Applicants are unable to trace the submission of documents or find out the status of their applications in the system. The development of an electronic tracking tool will allow applications to be efficiently traced. Applicants would be able to log into the system using a user specific password and information relating to the application can then viewed. This system will also prevent the numerous follow up emails and telephone calls that are made to the health authority in out to determine product status. ? One of the reasons that regulatory pharmacists seek other sources of information for compilation of the GPI is because the local OPI is outdated. The creation of an electronic access portal that contains the currently registered local and overseas OPIs and GPIs for all molecules, as well as the status of any pending amendments would allow applicants to view the status of already registered OPIs and GPIs. This would assist applicants in determining whether there is a pending amendment on the current OPI that was obtained in the commercial pack. Applicants may then refer to the pending amendment in the submission of the GPI. The portal should allow the public to gain access to the latest available PI for any product. ? The current SAHPRA system does not enforce any system for the updating of already approved PIs. This leaves the decision up to applicants who may choose not to update their PIs and hence the PI in the commercial pack may become outdated. The implementation of a mandatory updating system for all approved PIs will ensure that the commercial pack contains the latest approved PI. ? The regulatory staff stated that the communication channels between the applicant and SAHPRA are very poor. The improvement of communication channels would enhance the relationship between the applicant and the health authority. SAHPRA could consider using communication tools such as email and telephone calls to facilitate communication with the applicant. ? The current guidelines issued by SAHPRA for PI compilation lacks standardization and creates room for applicants to submit the GPI in different ways. The development of guidelines for the compilation of a GPI would assist pharmaceutical companies in standardising the applications that are submitted for review. This will assist evaluators as the quality of submissions will be improved through standardization. This could potentially aid in quicker review and approval timelines. ? The current SAHPRA system lacks transparency and openness. The implementation of public assessment reports would allow applicants to view the reasons for approval or rejection of an application. The inclusion of the name and contact details of the reviewer would allow applicants to be able to contact the reviewer in the event of a query. This would prevent the GPI from having to undergo multiple reviews and ultimately results in a decreased workload for both the health authority and the applicant. This could potentially lead to quicker review and approval timelines. ? The quality of the Clinical Committee Recommendations (CCRs) received from the health authority have been reported as poor. The provision of training to health authority evaluators and applicants by the health authority would improve the quality of CCRs and also standardise the clinical committee recommendations and applicant responses to the recommendations. This could aid applicants in understanding the requirements of the evaluators and ensure that the responses adequately meet these requirements. ? SAHPRA have confirmed that there is a lack of skilled resources. Head hunting and the employment of additional experienced staff members with agreed service level agreements will contribute to the efficient and timeous review of GPIs. ? The current SAHPRA system does not function optimally and at times submissions made by applicants are lost. The applicant may become of the lost documentation through follow up with the health authority. A fast track system should be considered for applications that were mislaid to ensure that these applications are not further delayed. ? There are no specific timelines for the review and approval of a GPI in South Africa. Benchmarking against foreign regulatory authorities that have specific review timelines and transparent review systems would ultimately result in the overall improvement of the current system. The EMA have stipulated timelines allocated to each stage of the medicine approval process (Kashyap, Gupta, & Ragunandanh, 2013). Figure 2 shows the allocation of timelines for the decentralised procedure used by the EMA. The use of a similar model in South Africa would be advantageous. Assessment Start of report from CHMP MAA Procedure (co)- provides (Day 1) Rappoteur comments (Day 70) (Day115) Comments by CHMP (Day 170) CHMP Decision on need of oral explanation by applicant (Day 180) Joint assessment report from (co)- rappoteur (Day 150) Oral explanation by applicant (Day 181) Restart Clock Submission of response by applicant (Day 121) Final Draft of english SPC,leaflet & labelling by applicant to co rappoteur, EMEA, CHMP (Day 185) CHMP opinion (Day 120) CHMP forwards to applicant list of questions (Day 120) Stop Clock Figure 2 Decentralised process with timelines ? The current SAHPRA system has no notification system. Applicants do not know if the GPI was successfully received, if the application is under review or if the GPI has been approved. The use of email notifications to applicants would allow applicants to immediately know the status of a GPI and they would to be able to communicate the product status to the greater business. Knowing the status of products in the system allows applicants to be able to efficiently plan their commercial strategies. This becomes very important with the launch of first to market generics where timing becomes crucial. This would encourage a sense of accountability of the part of the health authority. Figure 3 proposes stages at which the health authority should send out notifications to the applicant. GPI Response GPI CCR received GPI received allocated for review issued from approved applicant Figure 1 Proposed stages of email notifications ? The regulatory pharmacists have expressed that mistakes can happen through manual typing of the GPI. Generic pharmaceutical companies should consider employing administrative staff to type up word versions of the OPI, or invest in electronic tools that could carry out this process. The word version must be checked for accuracy prior to being used for compilation of the GPI. This would eliminate the potential for errors in the text. The above recommendations would improve the transparency of the process and would facilitate the timeous review of generic medicine PIs. The mandatory updating of approved PIs would allow for the alignment of information presented in the GPI and OPI. The local health authority is in a period of transition. The change from MCC to SAHPRA creates an opportunity for the implementation of amendments to current guidelines and systems. There are no current timelines for the review and approval of a GPI. This results in GPIs being evaluated many years after their initial submission. A generic medicine can only be approved by SAHPRA once all the areas of safety, quality and efficacy have been adequately addressed. The GPI is one of the components of registration that must be approved before the registration of a medicine. Since this process is currently taking so long, access to generic medicines is being delayed. The recommendations of this study suggest ways in which the review and approval process can be improved and essentially accelerated. Many patients and health care providers may be hesitant to use generic medicine however this study shows that in many instances the GPI contained the latest safety information that was not present in the OPI. The results of this study provide data that show that this is the case. This information could therefore potentially assist in improving the access and acceptance of generic medicines. This study focused on a single pharmaceutical company. Further research conducted on GPIs registered and the regulatory processes followed by other pharmaceutical companies would be useful in determining if the results are consistent with the findings of this research. Similar research using a larger sample size in other therapeutic classes of medicines would also be useful in determining the consistency of the research findings. 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CHAPTER 1: INTRODUCTION 1.1 Context for this study Access to medicine for the treatment of illnesses is an essential component of any healthcare system. Many people need to take medication on a daily basis. South Africa's health care

system faces many challenges and hence the system struggles to function as optimally as it could (Mayosi, Fisher, Lalloo, Sitas, & Tollman, 2009). The high cost of medicine remains a barrier for most of the South African population (Bangalee, 2015). One area in health care that has been identified to improve access is the use of generic substitution practices which has been identified as a mechanism that can contain costs (Karim, Pillai, Ziqubu-Page , Cassimjee, & Morar, 1996). This has been supported by legislation that allows for the generic substitution of originator medicines with generic medicines, on condition that the substitution is permitted by the patient (Bangalee, 2015). But, the availability of generic medicines does come with its own set of potential problems which create doubt and a lack of confidence with the use of generic medicines. This research aims to describe some of the problems that have been identified with the use of generic medicine with a focus on the PIs that are contained in the carton of a generic medicine. The findings of this study provide information that can assist with improving the access and acceptance of generic medicines. 1.1.1 Generic medicines A generic medicine is defined by the World Health Organization (WHO), as "a pharmaceutical product, usually intended to be interchangeable with an originator product. The generic medicine is manufactured without a license from the originator company and marketed after the expiry date of the patent or other exclusive rights" (Alrasheedy, et al., 2014). While originator medicines must conform to strict safety, quality and efficacy measures prior to obtaining health authority approval, generic medicines must only prove quality and bioequivalence to the originator medicine. Thus, the requirements for a generic medicine are less stringent than those for the new chemical entity, and the costs of testing and launching a generic medicine are a fraction of research and development costs of originator medicines. Medicinal products are considered to be bioequivalent if, after they are administered in the same dose, the rate and extent of bioavailability and the effects with respect to safety and efficacy are the same as the originator. There is no need for companies applying for registration of generic medicine to repeat the clinical trial studies that were submitted for registration of the originator medicine. This is one of the reasons why generic medicines are available at a cheaper price than the originator medicine (Dunne, Shannon, Dunne, & Cullen, 2013). Generic medicines have the same active ingredient, dosage form, strength and route of administration as the originator medicine and thus the information gathered is applicable to the generic. 1.1.2 Generic medicine labelling The primary source of drug information used in South Africa is the approved medicine PI. Generic pharmaceutical companies extract the safety and efficacy information directly from the PI of the originator medicine. Hence the information with respect to safety and efficacy provided in the PI of the generic medicine should be consistent with that provided in the originator medicine PI. The PI is a document that accompanies a medicine. It is intended to contribute to the safe and efficacious use of a medicine. It includes a scientific explanation of the uses for the medicine and its limitations which has been established by supporting data. It should be written in a manner that is not promotional, false or misleading. The information should be evidence based and updated from time to time as relevant pre- clinical and clinical data becomes available (Deepak, et al., 2013). The PI must be written in a manner that is clear and so that it can be understood by the general population (Al-Ramahi, Zaid, Kettana, Sweileh, &Al- Jabi, 2012). PIs are used as the primary source of medicine information by both the prescribers and the patient. Sometimes non-compliance in taking medication is because patients misunderstand instructions given by health care professionals. PIs then become a useful tool which conveys the verbal message (Morris & Halperin, 1979). However, some research has shown that PIs may impact patient compliance in an undesirable manner if the information that is provided is unreliable and incomplete (Dutta, Mahato, Saha, & Bhattacharyya, 2014). Incomplete and unreliable information could result in inconsistent prescribing patterns and may have a negative impact on patient safety and overall healthcare (Gharibyar, Sharif, Ghandour, Saffarini, & Aden, 2013). 1.1.3 Approval of Package inserts by the South African Health Authority Generic medicine can only be registered if it has met all the necessary standards as set out in the guidelines published by the local regulatory body (Sawalha, Sweileh, Zyoud, & Jabi, 2008). These include products that are of a high quality, and that is efficacious and safe for use in the intended population (Alrasheedy, et al., 2014). The South African Health Products Regulatory Authority (SAHPRA), previously known as the Medicines Control Council (MCC) has the task of evaluating and approving the information provided in the package insert (PI). This procedure takes place before the registration of the product. Once the PI has been approved, it cannot be changed unless approval from SAHPRA has been granted. The Medicines and Related Substances Act (Act no. 101 of 1965) and the general regulations made in terms of the Medicines and Related Substances Act (Act no. 101 of 1965), address the legal requirements that a PI be supplied with every medicine. Regulations 9 and 10 of Act 101 stipulate the minimum information requirements of the PI. Although the type of information provided under specific headings in the PI is mandated by SAHPRA, the process of compiling a PI or amending a PI is not always clear. The regulatory authority plays a key role in determining the contents of the PI however many health authorities, including SAHPRA have challenges that include limited human resources with skills oversight and system insufficiencies (MCC/MRA Backlog Task Team, 2010). 1.2 Literature review Whilst there has been some research conducted on PIs internationally, very little research has been done in South Africa. International and local research primarily focuses on the differences that have been noted in the various brands of generic medicine PIs (Filby, 2008). 1.2.1 International research Research that has been conducted internationally shows the following: The information in PIs is a source of information for patients which contributes to the safe and effective use of the medicine. However, this information is often lacking in consistency, completeness and is sometimes difficult to read and understand. An article published by Shrank and Avorn (2007), explored the potential and limitations of written drug information. Sources of written information available in the United States and the regulations that control the content of information were reviewed. Evidence shows that whilst patients prefer to receive medical information from health care providers, this is not actually what happens. The interaction between health care provider and patient is often inadequate. Patients often do not remember what was discussed and seek written information on how to use their medicine. An observation of medicine labelling showed that there was a lot of variability in the provided consumer medicine information (Shrank & Avorn, 2007). Prescribing materials from pharmaceuticals of the same drug within even one country was also found to show considerable differences. In 2003, Reggi et al conducted an international comparative study of different brands of the same drug in 26 countries (including America, Europe, Africa, Asia and Australasia). Three widely used drugs were selected: ciprofloxacin, fluoxetine and nifedipine. Results revealed that only two countries reflected all the indications for ciprofloxacin, three countries for fluoxetine and eleven for nifedipine. No countries reflected all the major side effects for nifedipine and fluoxetine and only one country reflected all the side effects for nifedipine. No countries listed all the precautions (Reggi, et al., 2003). Page 4 of 51 While the indications for a medicine may be different across countries there should be little difference in the listed warnings, precautions and contraindications. However, research has shown that this is not always the case. Pfistermeister et al (2013) conducted an in-depth comparison of the approved German, Swiss, British and US- American prescribing information of the top 10 prescribed psychiatric drugs. The comparison revealed that was a lot of variability in the important information across all the investigated markets. Health care providers who prescribe the same drug for the same medical condition in different countries are presented with different indications, warnings and special precautions or contraindications. When comparing the current medicine registration system in South Africa to other medicine registration systems in the world it becomes apparent that there are gaps in the current system being used by SAHPRA. The current medicine registration system in South Africa includes the issue of a product registration certificate once the health authority is satisfied that the medicine is proven to be safe, of good quality and is efficacious. The system does not include the provision of any additional public reports that provide information about the considerations that led the regulator to approve or refuse the application. As part of theEuropean Medicines Agency (EMA) and the Therapeutic Goods Administration (TGA) commitment to transparency, public assessment reports are provided upon completion of the review of a medicine (Papathanasiou, et al., 2016). Transparency and communication between the pharmaceutical company and the health authority during the approval process of medicine is crucial. The EMA guidance documents stipulate specific timelines for evaluation of a medicine application (Kashyap, Gupta, & Ragunandanh, 2013). Currently in South Africa there are no published timelines for registration. The lack of timelines would mean that a medicine could be in the registration process for

many years before obtaining approval. This also leads one to believe that there is no accountability on the part of the regulator and that medicines would not be registered as efficiently as they are in other parts of the world. South Africans would thus wait longer to have access to the same medicines that may already be available in other countries. Page 5 of 51 1.2.2. Local research Guidelines established by the South African health authority primarily focuses on the structure and content of the information provided under the different headings in the PI. There is very little guidance on the process of compilation that is to be followed and the sources of information to be used for the compilation of a generic medicine PI. The consequence of the lack of prescription in the documents results in regulatory pharmacists having to compile PIs differently using their years of experience in regulatory affairs as a guiding tool. In South Africa, negative perceptions exist surrounding the use of generic medicines (Patel, Gauld, Norris, & Rades, 2012). Research conducted by Patel et al (2012) explains that the perceptions of health care providers and patient consumers about the quality of generic medicines contributes to a lack in confidence in using them. Mohlala et al (2010) showed that the rate of prescribing drugs by their generic name in public and private health care facilities in 2 provinces in South Africa was as low as 45.2% in the public hospital and 24.5% by GPs (Mohlala, Peltzer, Phaswana-Mafuya, & Ramlagan, 2010). Whilst generic medicines are available in South Africa, patients and health care providers will only use them if they are confident in their safety, efficacy and quality. Two recent studies were conducted on generic medicine PIs in South Africa (Aziz 2017; Moodley 2016). The study that was carried out in 2016, concluded that PIs of approved products that are currently circulating show considerable differences between the originator product and subsequent generic brands of the same drug substance (Moodley, 2016). Another recent study that was carried out in 2017 evaluated the congruency of information in the patient information leaflet (PIL) as compared to the PI of 6 selected antihypertensive drugs. The study revealed a lack of congruency of key information (Aziz, 2017). This research adds to the small body of local research and provides insight into the differences noted between the PIs of originator and generic medicines; sources of information used by regulatory pharmacists, the regulatory process followed and the experiences gained during the compilation of a generic medicine PI for approval by the South African Health Product Regulatory Authority. 1.3 Problem statement The approval process for generic medicines is set at a lower threshold to enable generic companies to introduce drugs at affordable rates. The PI would be expected to mirror the originator PI as the generic company does not have the obligation to run clinical trials on efficacy and safety. But the timeline for registration in South Africa is long and contributes to a significant delay in access to generic medicines (Bateman, 2010). The processes followed for the compilation, assessment and approval of a generic medicine PI in South Africa is unclear. Previous research has identified inconsistencies in the information contained in PIs across brands of the same medicines (Pfistermeister, et al., 2013). These create doubt and a lack of confidence regarding the use of generic medicines. The findings of this study could contribute in assisting SAHPRA to amend and formulate better policies to regulate and approve generic medicine PIs. This will also aid in the better functioning of the pharmaceutical industry's regulatory departments. 1.4 Study aim and Objectives The aim of the study is to compare the PIs of originator and generic medicines of a small sample of medicines registered in South Africa and to determine the sources of information that are used to compile the generic medicine PI. The study also aims to explain the regulatory process followed by a pharmaceutical company to obtain approval of a generic medicine PI in South Africa. The objectives of the study are ? To describe the core differences between originator medicine PIs and generic medicine PIs with respect to the listed indications, contraindications, warnings, interactions, dosage and directions for use, side-effects and special precautions. ? To identify the process and the sources of information that regulatory personnel from one pharmaceutical company use to compile the generic medicine PI. ? To explore the experiences and perceptions of the regulatory staff from this pharmaceutical company with regard to compiling generic PIs for approval by SAHPRA. CHAPTER 2: METHODS 2.1 Introduction The study was conducted in two phases and a qualitative design was used. Qualitative research methods were used because they enabled the researcher to identify inconsistencies in the PIs through a textual analysis. Qualitative methods were appropriate to identify, describe, and understand the regulatory processes used by pharmacists at a specific pharmaceutical company. The regulatory processes involved in the compilation of a generic medicine PI includes the identification of the sources of information that are used and experiences that were gained during the compilation of a medicine PI. This chapter discusses the methods that were utilized to conduct this study. 2.2 Research site The pharmaceutical company that was selected as the research site is one of the world's leading generics and specialty pharmaceutical companies. It has products in approximately 140 countries and territories. The choice of this company as the research site is convenient as the researcher is employed at the pharmaceutical company. The researcher thus has access to the PIs registered by the company in order to conduct the comparative textual analysis. The researcher also has access to the regulatory pharmacists that compiled the PIs in order to conduct focus group discussions about the sources of information used and the regulatory process involved in compiling generic medicine PIs. 2.3 Phases of data collection There were two phases of data collection. The first was the identification and collection of PIs. Four medicines registered by the pharmaceutical company were identified. This data set was used to compare specific categories of the originator medicine PIs with the corresponding categories of the generic medicine PIs. The data set obtained from the first phase of data collection was used to address the first objective of the study i.e. To describe the differences between originator medicine PIs and generic medicine PIs with respect to the listed indications, contraindications, warnings, interactions, dosage and directions for use, side-effects and special precautions. The second phase of data collection was empirical. A focus group discussion was held with six members of the regulatory team employed at the pharmaceutical company. The data set obtained from the second phase of the study was used to address the remaining two objectives of the study; the process that regulatory pharmacists follow for the compilation of a PI, the sources of information that they draw on, and their perceptions and experiences of compiling generic medicine PIs for approval by SAHPRA. The researcher has ensured trustworthiness of the qualitative research by employing the use of triangulation between the data sets obtained from the different methods used in the study. Triangulation involves the use of different methods which form the major data collection strategies for qualitative research (Shenton, 2004). Triangulation using different methods makes provision for the credibility of the research and also reduces investigator bias thereby making provision for confirmability of the research. 2.4 Data Sets 2.4.1 Package Inserts Four generic medicines, two hypotensives and two tranquilisers, registered and marketed by the pharmaceutical company were selected and the PIs for these medicines were compared to the corresponding originator brand medicine PI registered in South Africa. The PIs of the selected medicines were sourced from the pharmaceutical company's regulatory affairs folder. The inclusion criteria for the drug selection were as follows: a) The generic medicine is currently being marketed in South Africa. b) The generic medicine was registered by the company in the last 5 years. The drugs selected for inclusion in the study are shown in Table 1. Table 1 Selected generic equivalent versus corresponding originator brand, molecule name and pharmacological classification Originator brand Generic equivalent* Molecule Pharmacological classification Atacand® GENERIC CANDESARTAN Candesartan cilexitil Hypotensive Micardis® GENERIC TELMISARTAN Telmisartan Hypotensive Seroquel® GENERIC QUETIAPINE Quetiapine fumarate Tranquiliser Zyprexa® GENERIC OLANZAPINE Olanzapine Tranquiliser * The trade names of the generic equivalent have been changed. Two medicines classified as hypotensives, Candesartan cilexitil and Telmisartan, and two medicines classified as tranquilisers, Quetiapine fumarate and Olanzapine were selected for analysis. These classes of drugs are widely and commonly used in South Africa. Both these classes of medicines are used for the treatment of chronic conditions and contribute to the utilization of a large number of medicines in the South Africa market. Two divergent markets were compared i.e. Cardiovascular and Central Nervous System. Medicines with different pharmacological classifications were selected so that the research would be able to accommodate more than only one category of medicine registered at the company. The results obtained would then be an indication of medicines that were registered across the business and not only to a specific class of medicine. Specific categories within the PIs were selected for analyses. These are the listed indications, recommended dosage, special precautions, contraindications, side-effects, interactions and warnings. These categories were selected because these sections contain information that are regarded as the most important for the health

care provider and the patient (Filby, 2008). 2.4.2 Focus group A focus group discussion was conducted with the regulatory staff of the company. Focus group discussion is a qualitative research method. This method allows an interviewer to ask study participants specific questions about a topic. This method is an appropriate choice for the research being conducted because it would provide the added dimension of interaction among study participants (Wong, 2008). Focus group discussions have been criticised for the vulnerability to bias. If there are dominant member/s in the group, it is advised that the interviewer should be aware of how the thoughts and ideas of these group members may influence the group. To deal with this criticism the researcher used the turn-taking approach. This approach ensured that each participant had a turn to contribute to the discussion. The focus group consisted of six participants employed at the company, viz. four registration pharmacists and two regulatory affairs officers. The pharmacists, including the regulatory affairs director, regulatory manager, and officers participating in the focus group, are all actively involved in the direct compilation of generic PIs. The participants and their qualifications are provided in Table 2. The regulatory staff have been employed at the pharmaceutical company for at least two years and have a lot of experience in the compilation of generic medicine PIs. Table 2 Participants of the focus group and their qualifications Name* Qualification No. of years employed in regulatory department Job title Lynn Bachelor of Pharmacy, Master of Science in Medicine (Pharmaceutical Affairs) 6 Regulatory Affairs Director and Responsible Pharmacist Carol Non-pharmaceutical 10 Regulatory Affairs Manager Bridget Bachelor of Pharmacy 3 Regulatory Affairs Pharmacist Miya Bachelor of Pharmacy, Master of Science in Medicine (Pharmaceutical Affairs) 5 Senior Regulatory Affairs Pharmacist and Responsible Pharmacist Tammy Bachelor of Pharmacy 2 Senior Regulatory Affairs Pharmacist Thea Qualified post basic pharmacist assistant 6 Senior Regulatory Affairs Officer * pseudonyms have been used. The focus group discussion focused on the following topics (see Appendix B): The results obtained in analysis of the comparison between the originator PI (OPI) and generic PI (GPI); the generic medicines registered by the company; the process followed to register a product, the sources of information used and the experiences the pharmacists had gained over time in the compilation of generic medicine PIs for approval by SAHPRA. The discussions were audio recorded and transcribed to facilitate data analysis. The focus group discussion was conducted in the boardroom at the pharmaceutical company. The venue was quiet, comfortable and convenient. The focus group participants sat at a table and were able to see and hear one another clearly. 2.5 Ethical considerations Approval to conduct the study was obtained from the Witwatersrand Human Research Ethics Committee prior to conducting this study (see Appendix C). The researcher obtained permission from the research site. Informed consent was obtained from all the participants of the study. 2.6 Data analysis 2.6.1 Package inserts A checklist was developed to record the differences in text noted in the selected categories of the generic medicine package and the originator medicine PI (see Appendix A). The following categories contained in the PI were compared and reviewed: - Indications - Contraindications - Warnings - Interactions - Dosage and directions for use - Side-effects - Special Precautions A manual comparative textual analysis was conducted on the differences that were noted on the checklist. 2.6.2 Focus group discussion The audio recorded focus group discussion was transcribed. A thematic content analysis was used to analyze the discussion. Thematic content analysis is a method of data analysis that is used to identify common themes that exist in the text (Burnard, Gill, Stewart, Treasure & Chadwick, 2008). The results of the textual comparisons were triangulated with the information obtained in the focus group interview. CHAPTER 3 RESULTS AND DISCUSSION A generic medicine is expected to provide the same therapeutic effect as the corresponding originator medicine (Dunne, Shannon, Dunne, & Cullen, 2013). Hence the information provided in an originator medicine PI and its corresponding generic medicine package is expected to be the same. The results of this study show that there are considerable differences between the information presented in the PIs. These differences stem from the sources of information that were used to compile the GPI and the regulatory challenges personnel face in obtaining approval of the GPI. In the context of this research the applicant is the pharmaceutical company that has applied to SAHPRA for registration of a generic medicine. 3.1 Comparative textual analysis of the OPI and GPI 3.1.1 Indications A comparison of the indications listed in the GPI and OPI of the four selected medicines revealed only one minor difference for one product, GENERIC OLANZAPINE. Table 3 shows that the phrase "in controlled trials" was removed from the indication however the indication for schizophrenia was still listed. The elimination of the words "in controlled trials" was discussed with participants of the focus group. Miya commented that, "the health authority evaluators always remove the reference to clinical trials". The participants of the focus group believe that the reason for removing the words clinical trials is because clinical trials are not conducted using generic medicines and hence it is incorrect to state this on the GPI even though it is stated on the OPI. The removal of clinical information by the regulatory staff and by the health authority evaluators is of major concern. Generic medicine manufacturers do not repeat the clinical studies that were performed by the originator company and the safety and efficacy profile of the generic medicine should mimic that of the originator medicine as the molecule contained in both medicines is exactly the same. Table 5, 6 and 9 show a similar pattern where clinical and non-clinical information was removed in the PIs of GENERIC OLANZAPINE and GENERIC QUETIAPINE. Upon analysis of the generic PIs that were Page 16 of 51 evaluated, it is evident that the information on clinical and non-clinical trial information has been removed. Table 3 Core differences between the OPI and GPI noted under the heading of Indications 3.1.2 Contraindications A comparison of the contraindications listed in the GPI and OPI revealed significant differences. Table 4 shows that the GPIs include several important contraindications that have not been listed on the PIs. The GPIs were shown to be more of a comprehensive source of information when compared to the OPIs. Three out of the four medicines had listed additional contraindications in the GPI that were not listed in the OPI. GENERIC OLANZAPINE was the only medicine whose contraindications matched those in the OPI. For one medicine, GENERIC CANDESARTAN, hepatic impairment was not listed as a contraindication whereas it was stated as a contraindication on the OPI. Another finding in the hypotensive class of medicines was that the limit for creatinine clearance was stated to be different in the GPIs compared to that stated in the OPIs i.e. 15 ml/min vs 30 ml/min. The implication of these differences is that the OPI would be able to be used in cases where the GPI is contraindicated. The different limits for creatinine clearance would mean that patients who had a creatinine clearance of 15 ml/min would not be able to use the GPI for treatment. However, this should not be possible because the molecule contained in the GPI and the OPI is identical and should be contraindicated in the same group of patients. The findings were discussed in the focus group and participants noted that it is common for the GPI to have more contraindications as well as more warnings, special precautions, interactions and side-effects than those listed in the OPI. It was agreed among participants that it is common for the GPI to have different limits for creatinine clearance than the limit stated in the OPI. The reason for these differences is because during the process of compiling a GPI, the regulatory staff align the GPI with the latest safety data that is available globally. Tammy explained that it is the company's responsibility to ensure that the GPI provides patients and health care providers with latest safety information even if the OPI does not contain this information. Miya said that, "the company could be sued should the medicine be used in a group of patients where it is contraindicated and the GPI does not mention this as a contraindication". There are a few reasons for the OPI not containing the latest information available globally. It is suggested that the originator company has applied for inclusion of additional contraindications into the OPI and this is under review at the health authority. It is a consideration that the originator company has not applied for inclusion of additional contraindications and the OPI has not been updated after registration was obtained. Both scenarios are possible. The lengthy evaluation timelines by the health authority may be holding up the update to the OPI since the originator company will not be able to update the OPI unless health authority approval is obtained. On the other hand, the originator company may not have applied for inclusion of the additional contraindications as the health authority does not routinely review the PIs of registered medicines and would not force the originator company to update its PI in line with latest safety information. Tammy explained that the latter is unlikely because the originator company is obligated to provide patients and health care providers with latest safety information. It is more likely that the originator company has applied for the inclusion of the additional information and has not obtained health authority approval as yet, hence the OPI is not as up to date as the GPI. These differences highlight a huge risk to patients and health care providers. Health care providers could prescribe the OPI

for patients in which the medicine is contraindicated. This could result in patient fatalities. Table 4 Core differences between the OPI and GPI noted under the heading of Contraindications 3.1.3 Warnings A comparison of the warnings listed in the GPI and OPI revealed that three out of the four medicines that were compared showed differences in the warnings that was provided. Table 5 shows that additional warnings were provided in the GPI for two of the medicines i.e. GENERIC CANDESARTAN and GENERIC QUETIAPINE. The Atacand® PI referred the patient to the specific section on pregnancy and lactation for warnings whereas the GPI PI stated the warning for pregnancy under the Warning heading. Thea said that, "this is not an uncommon finding and that the placement of the warning for pregnancy and lactation is dependent upon the health authority evaluator". Carol commented that "there is no clear guidance on whether it should be stated under the heading of warnings or under pregnancy in the PI". What stands out, is the lack in consistency as to where the information appears in the OPI versus where it appears in the GPI. Bridget said that, "it is ideal for patients to be able to refer to either PI and be able to locate the information in the same section rather than to have to find it under a different heading". Table 5 shows that the PI for GENERIC QUETIAPINE contained more warnings than that of the corresponding OPI. Again, it can be noted that the GPI is able to provide a more comprehensive list of warnings for the medicine. Tammy commented that "the additional warnings have been included in line with the latest originator medicine PI that was registered and approved overseas". The PI for GENERIC OLANZAPINE revealed that non-clinical data was removed in the GPI. Participants in the focus group explained that the removal of non-clinical data is requested by the SAHPRA evaluators because the registration of generic medicines do not require non-clinical studies to be submitted for evaluation and approval and that even though it is present in the OPI, it must be removed in the GPI. Non-clinical trials are performed to determine the pharmacokinetics, pharmacodynamics and safety profile of the drug. Non-clinical safety assessments are done by utilizing animal toxicological studies. The data from these studies are used to determine if there could be any potential safety risk when used in humans (TM, 2015). The information obtained during non - clinical trials determine the viability of progressing with further trials on the drug. Regulatory authorities across the world require non-clinical data prior to registration of an innovator medicine (Umscheid, Margolis, & Grossman, 2011). It is interesting to note that the originator company felt that this information was important enough to include into the OPI however this was removed in the GPI. The data obtained during non- clinical studies using originator drugs are applicable to generic medicines and should be included into the GPI. The registration of a generic medicine does not require clinical studies to be performed because they were already carried out using the originator medicine which contains the same active molecule. Hence the safety profile of the originator medicine is applicable to that of the generic medicine. Table 5 Core differences between the OPI and GPI noted under the heading of Warnings 3.1.4 Interactions A comparison of the interactions listed in the GPI and OPI revealed that all four medicines showed differences in the interactions that were listed. Miya explained that the global pharmacovigilance systems offer a platform for suspected interactions between medicines to be reported and investigated. The reporting of the suspected interactions happens after the registration of a medicine. The PI that is available globally would be updated in line with latest information that has been obtained from the global pharmacovigilance systems. This could be a reason why the interactions listed in the local OPI and the GPI are different. This difference could also be noted in the side- effects section of the PI. The WHO explains pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Pharmacovigilance has been expressed as a key component for effective drug regulation and has been cited as the worldwide master key for drug safety monitoring (Jeetu & Anusha, 2010). Miya commented that, "all generic companies have a pharmacovigilance department that record and investigate any adverse events that are reported by health care providers and patients". Often when an originator medicine becomes available on the market, only the interactions discovered during clinical trials are listed in the PI because these are the only known interactions that exist. When patients begin taking the medicine additional interactions are noted and can be picked by pharmacovigilance systems or post marketing studies. Miya thought that it was possible that the originator company may have applied for the local OPI to be updated but that, these changes may still be undergoing evaluation at the health authority level. Table 6 shows that the PI for GENERIC CANDESARTAN states the following, "Post marketing reports suggest a rare but significant interaction with increase of INR and bleeding with concomitant warfarin therapy ". This is an additional interaction between the concomitant use of warfarin and candesartan cilexitil. Although the OPI states that warfarin was investigated during clinical pharmacokinetic studies it does state that the concomitant use of these medicines leads to an increase in INR (International Normalised Ratio) and bleeding. This is a significant interaction and was listed in the GPI only. This data was derived from post marketing reports and included into the GPI by the regulatory affairs pharmacist that was compiling the GPI. Table 6 shows that an additional interaction listed for GENERIC TELMISARTAN was not listed in the OPI. The GPI stated that the concomitant treatment of telmisartan with non-steroidal anti-inflammatory drugs (NSAIDS) is associated with the potential for acute renal insufficiency in patients who are dehydrated and that patients receiving NSAIDS concomitantly with telmisartan need to be adequately hydrated. Health care providers who prescribe the OPI may not be aware of this interaction and could prescribe GENERIC CANDESARTAN for a patient who is not adequately hydrated and the patient would be at risk of developing renal problems. NSAIDs are very commonly used by patients and can be obtained as over the counter preparations at pharmacies. The PI for Seroquel® stated that the dose of Quetiapine would have to be reduced when taken with potent CYP34A inhibitors such as antifungals and macrolide antibiotics however the GPI stated that concomitant use of quetiapine and potent CYP34A inhibitors such as HIV protease inhibitors, azole antifungals and macrolide antibiotics were contraindicated. This finding is important because it illustrates that the GPI not only advises that the concomitant use of quetiapine and potent CYP34A inhibitors is contraindicated but it also provides more specific examples of CYP34A inhibitors. Human immunodeficiency virus (HIV) is very prevalent in South African and hence the inclusion of this information is vital. The GPI is also specific in noting the class of antifungals as azole antifungals whereas the OPI fails to do so. Again, the comparison of information between the OPI and GPI shows that the GPIs contained more comprehensive information. Table 6 shows the removal of statistical clinical trial information in the PI of GENERIC OLANZAPINE. The removal of clinical trial information was also noted in Table 1. Table 6 Core differences between the OPI and GPI noted under the heading of Interactions 3.1.5 Dosage and directions for use A comparison of the dosage and directions for use listed in the GPI and OPI revealed that only two medicines showed differences in the dosage and directions for use. Table 7 shows that GENERIC CANDESARTAN was contraindicated in patients with impaired renal function whereas the OPI advised using a lower dose of 4 mg. It is interesting to note that in Table 7 the OPI states that in patients with more severe renal impairment (i.e. creatinine clearance < 15 – 30 ml/min/1. 73 m2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be used however in Table 4 it lists severely impaired renal function as a contraindication. The normal corrected GFR is 80– 120 mL/min/1.73m2, impaired renal function is 30–80 mL/min/1.73m2 and renal failure is less than 30 mL/min/1.73m2 (Nankivell, 2001). The information provided in the OPI is not consistent within the different sections of the OPI. An additional statement was included into the dosage and directions for use of GENERIC OLANZAPINE. Tammy said that, "this data is included in line with latest safety data". The SAHPRA guidelines emphasize that the dosage and directions for use of the OPI and GPI should be the same. The WHO defines a generic medicine as a pharmaceutical product which is interchangeable with the originator brand product. Health care professionals will therefore prescribe and use the generic medicine in the same way as the originator product. Should the dosage and directions for use be different, this will have major consequences for treatment. A generic manufacturing company has the responsibility of ensuring that the information provided in the GPI is the same as that of the information provided in the PI of the originator medicine (Narang, 2016). The identical dosage and directions for use between the GPI and OPI would allow physicians to use the generic medicine with confidence. If the information provided under this section is different then it leads one to question whether the generic medicine is truly interchangeable with the originator brand product. As previously explained it is possible that the originator company may have applied for these changes to be made in the local OPI and these may still be under evaluation at the health authority. Table 7 Core differences between the OPI

and GPI noted under the heading of Dosage and Directions for use 3.1.6 Side-effects A comparison of the side-effects listed in the GPI and OPI revealed that all four medicines showed differences in the side-effects that were listed. Many additional side- effects were included into the GPI. Miya said that, "this finding is expected and that pharmacovigilance systems contribute to the inclusion of the additional side-effects". The frequency of the side-effects is mentioned in all of the generic PIs where they may previously not have been mentioned in the OPI. The side-effect listed in the GPI would Page 23 of 51 be classified under a different heading as compared to the heading in the OPI. Table 8 shows that in the PI of Atacand® angio-oedema was listed as a side effect under the heading skin and subcutaneous tissue disorders with no indication of frequency whereas it is listed on the GPI as an Immune system disorder as less frequent: Angioedema. Miya explained that this is not uncommon and that generic medicine PIs may reflect a frequency and heading that is listed in line with data in the overseas OPI. At the time of compiling a generic medicine PI the regulatory staff would use the latest available information from available reference sources to classify the heading and include the frequency of the side-effect. Tammy said that the, "additional side-effects present in the overseas OPI is also included at the same time". The comparison of the side-effects listed in Table 8 showed that the GPIs had a more extensive side-effect profile. The PI for GENERIC QUETIAPINE showed many differences to the OPI Zyprexa®. The body system category under which the side-effect was listed was very different to the OPI. There were many additional side effects listed under each of the headings. For example, in Table 8, the OPI Zyprexa® stated under the body system musculoskeletal, side-effect: rhabdomyolysis. In the GPI, this was stated under the body system musculoskeletal, connective tissue and bone disorders, side effect: less frequent: Extremity pain, join paint, back pain, rhabdomyolysis. Patients who may be switched from the originator medicine to the generic medicine might be hesitant to use the generic medicine as they may believe that generic medicine causes more side effects and is less safe than the originator medicine because it causes more side effects. Table 8 Core differences between the OPI and GPI noted under the heading of Side- effects 3.1.7 Special precautions A comparison of the special precautions listed in the GPI and OPI revealed that all medicines showed differences in the special precautions that were listed. Table 9 shows that additional special precautions were listed in the GPI of GENERIC QUETIAPINE and GENERIC OLANZAPINE. Bridget said that, "the special precautions in the GPI are aligned to global safety data available in the overseas OPI that is used when compiling the local GPI". In the hypotensive group of medicines, the generic medicine was contraindicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy. The OPIs had listed this as a special precaution and not as a contraindication. Another significant finding for GENERIC TELMISARTAN was that concomitant use of potassium sparing diuretics and GENERIC TELMISARTAN was not recommended whereas the OPI advised that potassium sparing diuretics should be used in caution with the originator medicine. This conflicting information means that the originator medicine could be used cautiously whilst the generic medicine is contraindicated. This should not be possible because the molecule contained in both the generic and originator medicine is the same and the information provided in the OPI and GPI should be identical. It is well known that generic medicines contain the same active pharmaceutical ingredient (API) as that of the corresponding originator medicine. The API is responsible for having the desired biological effect (Gavura, 2012). This means that the since the active ingredient is the same in both the originator and generic medicines, both medicines should behave in the same way and result in the same desired effect. The inconsistency in the provision of information compromises health care providers and patients. Table 9 shows that withdrawal information was included into the PI of GENERIC QUETIAPINE. This information is useful when patients no longer require treatment. The OPI fails to provide such information. The medicine should be gradually withdrawn otherwise the patient could experience withdrawal symptoms. The OPI for olanzapine stated that blood pressure should be periodically measured in patients over 65 years of age because postural hypotension was infrequently observed during clinical trials. Table 9 shows that this information was removed in the GPI. Non- clinical information on carcinogens, mutagenesis and fertility was also removed in the GPI. The participants of the focus group explained that the removal of non-clinical information was requested by the health authority evaluator as the clinical trial was not conducted using the generic medicine. Generic medicine applications piggy back on the studies that were performed by originator companies and hence do not have to perform their own clinical studies (Dunne, Shannon, Dunne, & Cullen, 2013). For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product (Hari Das, Prasant, Steffi, & Naushad, 2013). Bioequivalence testing links the generic medicine to the clinical studies that were conducted by the originator drug. The clinical studies performed on originator hence become applicable to the generic medicine as well and should be included in the GPI. Non-clinical trials are performed to determine the pharmacokinetics, pharmacodynamics and safety profile of the drug. Non-clinical safety assessments are done by utilizing animal toxicological studies. The data from these studies are used to determine if there could be any potential safety risk when used in humans (TM, 2015). The data obtained during non- clinical studies using originator drugs are applicable to generic medicines and should be included into the GPI. Additional Information on plasma clearance in smokers and on lipids alterations was provided in the GPI. The removal of some information and addition of other information in the GPI showed a lack in consistency between the information presented in the GPI and the OPI. The special precautions listed for sorbitol, lactose and soya lecithin is important for patients who have an intolerance towards these excipients. The excipients contained in generic medicines may differ to those that have been used to manufacture originator medicines. This would explain why the special precaution does not appear on both the OPI and GPI. The excipients contained in the originator medicine has not been listed on the OPI and hence it is not known whether the originator medicine contains soya lecithin or lactose. The current SAHPRA guidelines state that the excipients contained in medicines must be listed on the PI. The fact that the excipients were not listed on the local OPI indicates that it had not been updated in line with current SAHPRA guidelines. Table 9 Core differences between the OPI and GPI noted under the heading of Special Precautions 3.2 Summary of the textual analysis (First data set) The comparisons between the OPIs and GPIs showed that there are differences in the information that is provided under the various headings that were analysed in the package inserts. The key findings have been summarised below. The OPI and its corresponding GPI are not consistent in the information that it provides to the health care providers and to patients. Research conducted internationally indicates that this finding is not unique and that there is a lot of variability in the important information across all the investigated markets (Pfistermeister, et al., 2013). The listed contraindications, warnings, interactions, side-effects and precautions are more comprehensively provided for in the GPI. The GPI was able to provide important latest information that was not present in the OPI. The additional information provided in the GPI resulted in a PI that was of improved quality when compared to the OPI. However, if a patient or health care provider had to compare the information provided in the GPI and OPI it would appear different. The removal of clinical and non-clinical information as requested by the health authority evaluators and the additional information presented in the GPI could make it seem that the generic medicine is not as safe because it lists more contraindications and has more warnings, side-effects and special precautions than the OPI. The removal of non-clinical data from the GPI is of concern as the registration of generic medicines is based on the clinical and non-clinical studies that have been carried out using the originator medicine. A generic medicine is manufactured with the intention of being an alternative more cost-effective option for Page 27 of 51 therapy but the differences noted between the OPIs and GPIs makes one question whether it really is equivalent to the originator medicines. This may affect physician and patient confidence with the use of generic medicines. 3.3 Sources of information used to compile a GPI SAHPRA guidelines do provide a list of reference sources that could be used for the compilation of a GPI. Discussions during the focus group generated additional sources of information that regulatory staff use to compile a GPI. Table 10 shows the reference sources listed by SAHPRA compared to the list of reference sources provided by the participants of the focus group. Table 10 Reference sources used for compilation of a GPI – SAHPRA recommended sources vs actual reference sources used SAHPRA recommended reference sources Actual reference sources used ? ? Most recently approved innovator PI Reference books: - Good & Gilman - Martindale - USP dispensing information ? ? ? Most recently approved originator PI available in the local commercial pack Reference books: -

Good & Gilman - Martindale - USP dispensing information Company core data sheet is only ? ? Company core data sheet is only considered if substantiated by relevant data on which it is based Other references or peer reviewed updated references, including information obtained from other ? considered if substantiated by relevant data on which it is based Other references or peer reviewed updated references, including information obtained from other regulatory authorities with which the Council aligns itself ? ? regulatory authorities with which the Council aligns itself SAHPRA monographs SAHPRA guidelines1 ? ? ? ? ? SAHPRA monographs SAHPRA guidelines Most recently approved originator PI available overseas Most recently approved PI for the same medicine that is being applied for, that has already received approval by overseas regulatory authorities Latest edition of the Summary of product characteristics (SmPC), mainly the United Kingdom version As per the SAHPRA guidelines, pharmaceutical companies are required to use the most recent approved originator PI (PI) as the reference for the compilation of a generic PI. The guidelines state that the indications, dosage and directions for use and the safety profile for a generic medicine should at least be in line with that of the originator PI. The guideline also states that SAHPRA retains the discretion to require more or less details under the respective headings of the PI. SAHPRA guidelines recommend that applicants use the reference book Goodman & Gilman, to include additional information relating to pharmacological action. The Martindale is used for additional information relating to safety information. Other supplementary reference sources may be used i.e. USP Dispensing information, SAHPRA monographs and peer reviews references. 1 SAHPRA guidelines for PIs comprise of the following guidelines: PIs for Human Medicines, 2014 Labelling of medicines containing sugars, 2015 Patient Information Leaflets, 2014 PIs for Human Medicines Standardised Texts, 2015 Carol explained that SAHPRA guidelines are used primarily for structure and layout of the GPI. The guidelines are also useful when standardised texts for a specific condition or class of medicine is required or for when the sugar content of the medicine needs to be included. Other than for the reasons stated above, the OPI that is available in the local commercial pack is the primary reference source that is used to compile the GPI. Carol emphasized that the approved OPI that is registered overseas and/or the UK Summary of Product Characteristics (SmPC) are used for compilation when the local originator PI is outdated and does not contain the most recent available safety data. The SmPC is obtained electronically via the electronic medicines compendium (eMC) website and the document contains up to date, approved and regulated prescribing and patient information for licensed medicines. All the participants of the focus group agreed that the information under the headings contraindications, side-effects, warnings and special precautions of the GPI are updated in line with the overseas OPI and/or the UK SmPC. A significant finding is that the regulatory staff align the GPI to the latest information that is available internationally. The reason for the alignment with international information is because the local OPI is outdated. The company has its own set of global standards which has to ensure that the patient is protected from receiving outdated information, that the company is protected from reputational damage and that there is consistency in the labelling information in all products that are marketed internationally. The company is at a risk of being sued should important information be left out of the GPI. 3.4 Processes followed in the compilation of a GPI 3.4.1 Health authority process The health authority has not published a process for the compilation of a GPI. Guidelines have been published that provide information on the structure and content of the PI, however, the actual process has not been documented. Further to this there are no timelines allocated to the evaluation process. Once a GPI has been submitted for evaluation, there is no information provided as to when the pharmaceutical company Page 30 of 51 can expect an outcome. Carol said that "it could around 4 years to receive the first clinical committee recommendation". 3.4.2 Internal process The focus group discussion revealed that there is agreement among the pharmacists about the process that is followed to compile GPIs. The process can be summarised into eight steps, refer Figure 1. Carol confirmed that the internal process that is described below has been developed by the regulatory staff through experience. Step 1 Obtain OPI Obtain the latest originator PI from the South African commercial pack. Step 2 Retype OPI Retype the originator PI into a word document. Step 3 Replace Trade Name Replace the trade name of the originator medicine with the trade name of the generic medicine. Step 4 Amend in line with dossier information Amend the excipients, identification, presentation of the commercial pack and storage conditions so as to be in line with the information available in the generic medicine dossier Remove or reword information regarding the clinical studies conducted by the originator company depending on the content. Step 5 Check against latest reference sources Check this version of the GPI against the approved overseas OPI, UK SmPC and recommended reference books. Include any additional information. Step 6 Check indications Check the indications to ensure that there is no local patent protection on any specific indication. Remove any indication where a patent still exists. Step 7 Submit for review Submit the GPI as part of the dossier for approval by SAHPRA Step 8 Recieve CCRs and respond until GPI is approved Receive a Clinical Committee Recommendation (CCR) once the GPI has been evaluated by the clinical unit of SAHPRA. The CCR contains the evaluators' comments and suggestions after evaluating the GPI. Respond to and correct the GPI in line with the committee's comments. Resubmit the GPI for a second evaluation. Subsequent CCRs may be received until the GPI is approved by the clinical committee. Figure 1 Eight steps of GPI compilation 3.4.3 Amendment process The PI of registered medicines can only be changed or amended upon approval from SAHPRA. SAHPRA has provided an amendments guideline that allows for amendments to be done on registered medicines, however, there is no guidance on timelines for approval. Carol said that, "it could take around 1 ½ years for the applicant to receive any outcome". Bridget commented that "there is no process for regulatory staff to contact SAHPRA to find out if there is an outstanding amendment on a medicine". This provides a possible explanation as to why the local OPIs that were used in the textual analysis did not contain all the latest safety information that the GPI contained. It is possible the originator company has applied for an amendment to the OPI, however, they have not received any outcome from the health authority and hence are unable to update their PI. 3.5 Experiences and perceptions of regulatory affairs personnel 3.5.1 Accessibility of the local OPI During the focus group discussion, the participants explained that whilst the most recent local originator PI is the primary reference to be used for the compilation of a generic medicine PI, it is very difficult to obtain the most recent version. Often the PI that is available in the commercial pack of the originator medicine in South Africa is outdated and not in line with the corresponding overseas originator PI or UK SmPC. Bridget said that, "the compiler will include the latest updated information from the overseas originator PI and/or the UK SmPC into the GPI in order to ensure that the generic medicine PI contains the latest information". The latest safety information from acceptable reference books will also be included to ensure that the GPI contains the most updated information available at the time. This is often the reason why differences arise in the information presented in the OPI and the GPI. This is also the main reason why the side effect profile, warnings and special precautions of the generic medicine is more extensive than that of the local originator medicine. In the European Union (EU) and the United States (US), it is a requirement for originator companies to update their PIs in line with phase IV clinical trial data, pharmacovigilance data and ongoing research (Filby, 2007). It is therefore also possible that an amendment may have been submitted by the originator company, to SAHPRA to update the information that is available in the local OPI available in the commercial pack. Miya said that, "due to long timelines for review by SAHPRA the amendment may not be reviewed for many years and hence the originator medicine PI available in South Africa will not be in line with the latest information that is available globally". The generic pharmaceutical company will also not have oversight of the pending amendment on the OPI as there is no system in place to gain access to this information. 3.5.2 Administrative issues One of the issues that emerged from the focus group was the room for error in the procedure because the local OPI is retyped into a word document. Thea said that, "there is a possibility for errors to be made and for information to be missed out or repeated". Thea and Lynn said that, "due to time constraints, the word document may not be peer reviewed and hence the error will be submitted in the final version of the GPI". SAHPRA evaluators may not pick up this error during evaluation and this will lead to the information that is present in the OPI being different to that presented in the GPI. Thea, Bridget and Tammy said that, "they experience a lot of frustration in retyping an OPI into a word version for editing". Longer complex medicine PI e.g. antiretroviral medicines (a combination of multiple active ingredients) PIs are at greater risk due to the amount of information that needs to be retyped. Thea described the process as time consuming and exhausting. 3.5.3 Patent issues

Another issue that was raised by Carol was around patent issues which SAHPRA does not concern itself with. Bridget said that, "it is the responsibility of the company to ensure that the patent issues are checked prior to product launch". Currently regulatory staff at the company remove indications due to an existing patent. This is a patent protection strategy that originator companies use to ensure market exclusivity. Hence the approved GPI may not contain some of the indications present in the OPI due to patent protection. Due to the long timelines for review, the regulatory staff find that once the GPI is approved, the patent on the indication has already expired and an application to include the indication on the GPI then needs to be submitted to SAHPRA for approval. This means that the product would be launched without the indication being listed on the GPI and only once approval has been obtained from SAHPRA can the indication be added into the GPI. Carol explained that as per the company's global policy all indications should be applied for at once and then prior to launch the applicant should remove those indications that have patents and only include them onto the PI once the patent has expired. The process of removing patented indications is internally referred to as "Carving". If SAHPRA were to implement this system it would prevent another application having to be submitted in order to add a new indication. This would lead to a decreased workload on the side of the health authority and on the regulatory staff of the company. It would also allow for the generic medicine to be used for an additional indication as soon as patent expiry without having to wait for approval from the health authority. 3.5.4 Challenges in dealing with the health authority All the regulatory staff described the process of compiling and submitting a GPI for approval by SAHPRA as frustrating and inconsistent. Lynn felt strongly that the system lacks transparency, reproducibility and overall integrity. 3.5.4.1 Quality of the Clinical Committee Recommendation (CCR) The group noted that clinical committee recommendations received from the evaluators are often inconsistent. Bridget, Tammy and Thea said that, "the information that has been requested for inclusion in the first CCR received from evaluators is asked to be removed in the second CCR". There is no reason or justification given for the removal. This leads to a lot of frustration as the staff member compiling the PI does not know why the evaluator is requesting the removal. Lynn said that, "a possible reason for this is that the PI is not reviewed by the same evaluator each time and hence each evaluator will have a different opinion on whether the information should be present or not". The level of training and skill set of the evaluators are not known. The applicant has to comply with the recommendations of the evaluators or face a further delay in approval. Lynn said that, "the allocation of a specific product to a specific team of evaluators rather than to any available evaluator would reduce the number of inconsistencies received in CCR". Carol said that, "It very unusual for a product to only receive one clinical recommendation". The product will most likely receive a second or third recommendation for information to be included or excluded or amended. This contributes to a very long delay in the approval of a GPI. Most times the second or third recommendations focus on spelling or the inclusion of a comma or a full stop. The focus of the evaluation shifts from actual medical content to finding spelling and grammar errors. All the participants of the focus group agreed that delaying a product's approval because of a full stop, comma or spelling mistake is extremely frustrating as the applicant could wait a further 3 – 6 months in order to gain clinical approval. Tammy said that, "at times, clinical committee recommendations request the applicant to justify statements that were taken directly from the OPI. It is possible that the OPI may not have been updated to the latest information available but the information was included since it is presented in the commercially available OPI. Thea explained that there are situations were recommendations received from the pharmaceutical and analytical unit mimic that received from the clinical unit. This results in a duplication of work. Communication between the different units of the health authority would prevent this from occurring and would also save time and resource for the health authority and the applicant. Lynn said that, "the GPIs are also manually assessed and the evaluators comments are written in pen on a hard copy of the GPI". The annotated GPI is then sent to the applicant. At times, staff members are unable to decipher what has been written on the GPI or what needs to be corrected. The comments are vague and the staff member compiling the response is left to interpret what he or she thinks is correct and respond accordingly. Should the regulatory staff misinterpret what is required then an additional CCR would follow leading to a further delay in approval. 3.5.4.2 Communication and transparency Carol said that, "there is no opportunity for a regulatory staff member to contact or approach the evaluator". The staff members explained that when they try to call or email SAHPRA they are often unsuccessful. If somebody does answer the phone, they are at most times unable to assist or hesitant to assist. Lynn said that, "it is not possible to know the names of the evaluators or to speak or contact them directly. The process is not transparent and it is difficult to follow up on the approval of products or even to determine product status". Foreign regulatory authorities employ the use of more transparent review systems. As discussed in the literature review, both the TGA and the EMA provide public assessment reports upon review completion. The timelines for assessment by the EMA are clearly defined. Applicants are allowed to contact the evaluator during the approval process. A meeting or telephone call is arranged to discuss any queries. The above issues ultimately highlight the impact that the evaluator has on the overall approval process. Lynn said that, "if evaluators were accessible this would allow applicants to contact them directly and set up meetings or telephone calls to discuss Page 37 of 51 questions raised by the applicant". This would favour approval timelines instead of receiving numerous CCRs and would also lead to decreased work load for the applicant and the health authority. Tammy and Bridget said, "that there have been cases where the responses to clinical recommendations have been mislaid". They had received no communication from the health authority that the response has been mislaid. This was discovered when they had contacted the health authority via telephone in order to obtain a product status. No subsequent written communication was received. Thea and Bridget had to resubmit the response and this contributed to a further delay in obtaining approval. The health authority did not fast track this response and it waited in the queue for assessment. 3.5.4.3 Amendments Lynn said that, "the amendments of currently approved PIs also take a very long time for approval". Companies may need to do multiple updates to PIs and find themselves in a situation where the last amendment was not as yet approved and they already have to submit a new amendment. This causes a lot of confusion and results in the GPI that is present in the commercial pack being outdated and not in line with the foreign GPI available in overseas countries for the same product. This poses a risk as patients in South Africa do not have access to latest available medicine information. 3.5.4.4 Clinical committee meeting dates Currently clinical committee meetings are held at set dates that are determined by the health authority. This results in outcomes for multiple products being received at the same time. Lynn said that, "it would be useful if products could be discussed sooner rather than waiting for a clinical meeting date". This would allow applicants to receive recommendations as soon as they become available from evaluators. This would ultimately shorten the timelines for approval. Carol said that, "the current system needs to be revised". 3.5.4.5 Health authority backlog The health authority has acknowledged that a backlog exists and that the evaluation of products have been delayed. This is attributed to a lack of skilled staff and also due to a lack of service level agreements between the external evaluators reviewing the PIs and the health authority. Lynn said that, "the lack of proper evaluation and review systems coupled with human resource challenges contribute to the current backlog and hence the review process takes a long time to complete". 3.6 Summary of the focus group discussions (Second Data Set) The focus group discussion was conducted with regulatory affairs personnel who identified the sources of information that are used to compile the GPI. SAHPRA have recommended a list of sources that must be used to compile a GPI, however, the regulatory affairs personnel use additional sources of information to compile the GPI. The inclusion of additional information from additional sources results in a difference in the information that is provided in the GPI. The information that is included into the GPI is in line with the latest overseas OPI and/or the UK SmPC. The regulatory staff have had to use these additional resources for information as the primary source as recommended by SAHPRA, the local OPI, is considered outdated due to the omission of the latest product information available in the overseas OPI and UK SmPC. These findings are noted in the OPI for Atacand® in which the date of PI publication is listed as 30 November 2007. This date indicates that the OPI was last updated approximately 10 years ago. The regulatory affairs personnel identified the process that was used for the compilation of a GPI. The process used was described in eight steps. Currently SAHPRA have not recommended a process for the compilation of a GPI. The regulatory personnel have formulated these steps through their years of experience in compiling GPIs. Since SAHPRA have not

recommended a process, the staff had to formulate their own process in order to ensure consistency of GPI compilations within the pharmaceutical company. The timeline for evaluation of a GPI and subsequent receipt of a clinical committee recommendation by the applicant is unknown. The process of amending a PI that has already gained SAHPRA approval is challenging and there are no clear timelines on how long this process can take. This could be a reason that explains why the local OPIs have been not been updated. The experiences and perceptions of the regulatory affairs personnel in compiling a GPI for approval by SAHPRA was explored. The regulatory staff have had many challenges in compiling the GPI, including accessibility to the latest local OPI. Due to the local OPI being outdated staff had to seek other sources of information to ensure that the GPI contained the most up to date information that is available globally. The staff also faced administrative issues. Manual typing up of the local OPI creates room for errors in the GPI. Applications to include additional indications into an approved GPI took long and resulted in an additional workload for both the applicant and the health authority. Another enormous challenge for the regulatory staff was the communication with the health authority. A GPI must undergo evaluation by the evaluators of the health authority prior to approval. The evaluators assess the GPI and determine which information should be deleted, added or amended. The review process is a contributor to the differences that were noted in the textual comparisons. The regulatory staff experience very poor levels of communication with the health authority. They are unable to contact the evaluators and even experience challenges in obtaining a product status via phone or email. There is no online system available to track or view the progress of a GPI that has been submitted for approval. The system lacks traceability and transparency. CHAPTER 4 CONCLUSIONS AND RECOMMENDATIONS The study evaluated the differences noted between the information presented in the originator medicine PI and the generic medicine PI. This comparative analysis of the PIs was manually performed using checklists. A focus group discussion was conducted with regulatory staff participants, involved in the compilation of generic medicine PIs, from one pharmaceutical company. The participants are involved in the compilation of generic medicine PIs. The differences noted in the textual analysis was discussed in the focus group. The sources of information that are used and the regulatory process that is followed for the compilation of a generic medicine PI was identified. The study explored the experiences and perceptions of the regulatory staff with regard to compiling a generic medicine PI for approval by the South African Health Product Authority. 4.1 Summary of findings As mandated by SAHPRA, the contents of a generic medicine PI (GPI) should be the same as that presented in the originator medicine PI because its compilation is based on the information present in the OPI. The results of the comparative textual analysis showed that this is not the case. The analysis showed that there was a large number of differences between the information presented in generic and originator medicine PIs. The GPI contained additional information under the various headings of the PI i.e. Contraindications, warnings, interactions, side-effects and special precautions. The additional information presented in the GPI was included by regulatory pharmacists who were responsible for the compilation of the GPI. The information was obtained from the latest information that was available in the list of reference sources used by the regulatory affairs staff (refer Table 10). The information that was included into the GPI was important to both the health care provider and the patient. The inclusion of additional latest information into the GPI resulted in it being a more comprehensive and accurate source of information than the OPI. Although the GPI was shown to contain vital information that the OPI lacked, it does eventually result in different information being provided in PI sources that are expected to be the same. The exclusion of clinical and non-clinical data accompanied with the comprehensive side- effect profile, additional contraindications, warnings, interactions and special precautions may lead one to believe that the generic medicine is not the same as the originator medicine even though the molecule contained in originator and the registered generic medicine is the same. It could also be perceived that the generic medicine is less safe because it has more side effects and more contraindications, warnings, interactions and special precautions. Patients may also believe that this is the reason why generic medicine is available at a cheaper price. It is therefore ironic that the increased quality of the GPI may undermine patient confidence when deciding to use generic medicines. The study found that the differences noted in the OPI and GPI could be attributed to the sources of information used to compile the GPI and the health authority review process. SAHPRA recommended that the latest locally available OPI be used as the primary source for compilation of the GPI, however, this is not what happens in practise. The local OPI is outdated and regulatory staff are then forced to seek alternative sources of information to ensure that the GPI contains the latest information that is available. Generic companies have to adhere to their own set of internal global standards and also need to ensure that they are not sued by patients should the information in the GPI be incorrect or inadequate. SAHPRA have not recommended a process for the compilation of a GPI or the amendment of an already registered GPI. Regulatory pharmacists draw on their regulatory experiences and decide on the best way of GPI compilation. The local health authority process is flawed and does not support the timeous registration and access to generic medicine. There are no confirmed timelines for the approval of a generic medicine PI or an amendment to an already registered GPI. The regulatory process for compilation and approval of a GPI is unclear. The manual assessment of the GPIs by the health authority evaluators as well as a lack in the standardisation of recommendations received results in many reviews of the GPI prior to approval being obtained. The lack of an electronic tracking tool makes it difficult to track and trace the status of a GPI. Communication channels with the staff of the health authority are limited and the interaction is often very poor. The lack of timelines and a Page 42 of 51 structured, transparent system for generic medicine review contributes to a delay in registration and ultimately a delay in access to generic medicine. 4.2 Recommendations The regulatory staff at the pharmaceutical company describe the process of compilation and approval of a GPI as inconsistent and frustrating. The following recommendations are proposed: ? The current SAHPRA system lacks transparency. Applicants are unable to trace the submission of documents or find out the status of their applications in the system. The development of an electronic tracking tool will allow applications to be efficiently traced. Applicants would be able to log into the system using a user specific password and information relating to the application can then viewed. This system will also prevent the numerous follow up emails and telephone calls that are made to the health authority in out to determine product status. ? One of the reasons that regulatory pharmacists seek other sources of information for compilation of the GPI is because the local OPI is outdated. The creation of an electronic access portal that contains the currently registered local and overseas OPIs and GPIs for all molecules, as well as the status of any pending amendments would allow applicants to view the status of already registered OPIs and GPIs. This would assist applicants in determining whether there is a pending amendment on the current OPI that was obtained in the commercial pack. Applicants may then refer to the pending amendment in the submission of the GPI. The portal should allow the public to gain access to the latest available PI for any product. ? The current SAHPRA system does not enforce any system for the updating of already approved PIs. This leaves the decision up to applicants who may choose not to update their PIs and hence the PI in the commercial pack may become outdated. The implementation of a mandatory updating system for all approved PIs will ensure that the commercial pack contains the latest approved PI. ? The regulatory staff stated that the communication channels between the applicant and SAHPRA are very poor. The improvement of communication channels would enhance the relationship between the applicant and the health authority. SAHPRA could consider using communication tools such as email and telephone calls to facilitate communication with the applicant. ? The current guidelines issued by SAHPRA for PI compilation lacks standardization and creates room for applicants to submit the GPI in different ways. The development of guidelines for the compilation of a GPI would assist pharmaceutical companies in standardising the applications that are submitted for review. This will assist evaluators as the quality of submissions will be improved through standardization. This could potentially aid in quicker review and approval timelines. ? The current SAHPRA system lacks transparency and openness. The implementation of public assessment reports would allow applicants to view the reasons for approval or rejection of an application. The inclusion of the name and contact details of the reviewer would allow applicants to be able to contact the reviewer in the event of a query. This would prevent the GPI from having to undergo multiple reviews and ultimately results in a decreased workload for both the health authority and the applicant. This could potentially lead to quicker review and approval timelines. ? The quality of the Clinical Committee Recommendations (CCRs) received from the health authority have been

reported as poor. The provision of training to health authority evaluators and applicants by the health authority would improve the quality of CCRs and also standardise the clinical committee recommendations and applicant responses to the recommendations. This could aid applicants in understanding the requirements of the evaluators and ensure that the responses adequately meet these requirements. ? SAHPRA have confirmed that there is a lack of skilled resources. Head hunting and the employment of additional experienced staff members with agreed service level agreements will contribute to the efficient and timeous review of GPIs. ? The current SAHPRA system does not function optimally and at times submissions made by applicants are lost. The applicant may become of the lost documentation through follow up with the health authority. A fast track system should be considered for applications that were mislaid to ensure that these applications are not further delayed. ? There are no specific timelines for the review and approval of a GPI in South Africa. Benchmarking against foreign regulatory authorities that have specific review timelines and transparent review systems would ultimately result in the overall improvement of the current system. The EMA have stipulated timelines allocated to each stage of the medicine approval process (Kashyap, Gupta, & Ragunandanh, 2013). Figure 2 shows the allocation of timelines for the decentralised procedure used by the EMA. The use of a similar model in South Africa would be advantageous. Assessment Start of report from CHMP MAA Procedure (co)- provides (Day 1) Rappoteur comments (Day 70) (Day115) Comments by CHMP (Day 170) CHMP Decision on need of oral explanation by applicant (Day 180) Joint assessment report from (co)- rappoteur (Day 150) Oral explanation by applicant (Day 181) Restart Clock Submission of response by applicant (Day 121) Final Draft of english SPC,leaflet & labelling by applicant to co rappoteur, EMEA, CHMP (Day 185) CHMP opinion (Day 120) CHMP forwards to applicant list of questions (Day 120) Stop Clock Figure 2 Decentralised process with timelines ? The current SAHPRA system has no notification system. Applicants do not know if the GPI was successfully received, if the application is under review or if the GPI has been approved. The use of email notifications to applicants would allow applicants to immediately know the status of a GPI and they would to be able to communicate the product status to the greater business. Knowing the status of products in the system allows applicants to be able to efficiently plan their commercial strategies. This becomes very important with the launch of first to market generics where timing becomes crucial. This would encourage a sense of accountability of the part of the health authority. Figure 3 proposes stages at which the health authority should send out notifications to the applicant. GPI Response GPI CCR received GPI received allocated for review issued from approved applicant Figure 1 Proposed stages of email notifications ? The regulatory pharmacists have expressed that mistakes can happen through manual typing of the GPI. Generic pharmaceutical companies should consider employing administrative staff to type up word versions of the OPI, or invest in electronic tools that could carry out this process. The word version must be checked for accuracy prior to being used for compilation of the GPI. This would eliminate the potential for errors in the text. The above recommendations would improve the transparency of the process and would facilitate the timeous review of generic medicine PIs. The mandatory updating of approved PIs would allow for the alignment of information presented in the GPI and OPI. The local health authority is in a period of transition. The change from MCC to SAHPRA creates an opportunity for the implementation of amendments to current guidelines and systems. There are no current timelines for the review and approval of a GPI. This results in GPIs being evaluated many years after their initial submission. A generic medicine can only be approved by SAHPRA once all the areas of safety, quality and efficacy have been adequately addressed. The GPI is one of the components of registration that must be approved before the registration of a medicine. Since this process is currently taking so long, access to generic medicines is being delayed. The recommendations of this study suggest ways in which the review and approval process can be improved and essentially accelerated. Many patients and health care providers may be hesitant to use generic medicine however this study shows that in many instances the GPI contained the latest safety information that was not present in the OPI. The results of this study provide data that show that this is the case. This information could therefore potentially assist in improving the access and acceptance of generic medicines. This study focused on a single pharmaceutical company. Further research conducted on GPIs registered and the regulatory processes followed by other pharmaceutical companies would be useful in determining if the results are consistent with the findings of this research. Similar research using a larger sample size in other therapeutic classes of medicines would also be useful in determining the consistency of the research findings. It would also be interesting to conduct an analysis of PIs of the same products utilised in this study but sourced from different countries to establish if comparable findings are obtained. References Al-Ramahi, R., Zaid, A. N., Kettana, N., Sweileh, W., & Al-Jabi, D. (2012). Attitudes of consumers and healthcare professionals towards the patient PIs - a study in Palestine. Pharmacy Practice, 10: 57-63. Alrasheedy, A. A., Hassali , M. A., Stewart, K., Kong, D. C., Aljadhey, H., Ibrahim, M. M., & Al- Tamimi, S. K. (2014). Patient knowledge, perceptions, and acceptance of generic medicines: a comprehensive review of the current literature. Patient Intelligence, 6: 1- 29. Aziz, Z. (2017). Comparison of PIs and patient information leaflets: An in-depth analysis of prescribing information in Angiotensin receptor blockers marketed in South Africa. MSc research report, The University of Witwatersrand, Johannesburg South Africa. Bangalee, V. (2015). 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