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A comparative analysis of the innovator and generic package inserts for selected central nervous system medication in South Africa

Research Report in partial fulfillment of MSc (Med) Pharmaceutical Affairs

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Declaration

I, Kerusha Moodley, declare that this research report is my own work. It is being submitted for the degree of Master of Science (med) Pharmaceutical Affairs, at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other university.

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Abstract

The evolution of generic medicines has provided greater access to healthcare for the general population. But this has also given rise to disparities with respect to information that needs to accompany generic medicines. Generic companies face a major problem when bringing a new product to the market place. Access to the originators' clinical and post surveillance data is prohibited and not easily attainable. This data provides the basis of the labelling information and if copied, generic companies run the risk of copyright infringement which creates tension on how appropriate information is delivered. Consequently, generic manufacturers are forced to develop PIs. Previous studies indicate that this process yields a package insert of substandard quality with questionable quality, which leaves the impression that the pharmaceutical industry is more profit-driven than patient-driven. This is a comparative study of innovator and generic package inserts for molecules; fluoxetine, citalopram, sertraline, venlafaxine and risperidone. A textual analysis was used to compare package inserts. Key findings from this novel study demonstrate that there are considerable differences between the originator PI and the generic brands. Side effects experienced solely by women who are twice more likely than males to administer antidepressants were found to be omitted from two out of three generics. Limited access to correct information impedes the decision making process for the healthcare professional as well as the patient resulting in lack of confidence in the product itself. Other significant findings highlighted in this study revealed inconsistencies with respect to the use of words with opposing meanings, incorrect use of prefixes which ultimately shifts the meanings of words as well as the alteration of nouns which downplays the severity of side effects further emphasizing the variability of prescribing information currently available in South Africa. Ordering of risk within a package insert is an important factor in determining the risk profile conveyed by text. Deciphering the most important information from the less important information proves to be difficult with the package inserts analysed. The on-going trend depicts gaps in the South African registration system with respect to labelling of medicines and thus warrants urgent attention.

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Chapter 1: Introduction

Medication use in health for millions of people across the globe is an important component of universal health coverage. Total spending on medicines exceeded one trillion U.S dollars for the first time globally in 2014. Spending on generics will continue to increase; especially in emerging markets, and will account for 63% of the total global volume market, being between $370 - 400 billion at the end of 2017.[1] Allowing access to essential medicines is a constant concern especially in emerging or developing markets. This is even more vital in emerging markets, where access to health care resources is limited mainly by cost factors.

In order to allow greater access to medicines given the high cost of most branded or originator medicines, more affordable medication must be available. The evolution of generic medication fills this essential need. A medicine is considered a generic if it is interchangeable and multisource. Therefore it should be therapeutically and bio-equivalent to the innovator. If both medicines contain the same amount of active substances in the same dosage form; meet the same or comparable standards; are intended to be administered by the same route; and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, then these medicines are considered to be pharmaceutically equivalent.[2] However the excipients do not necessarily have to be the same. Generic drug applications are not required to include preclinical and clinical data to establish safety and effectiveness. It is for this reason that the Medicines Control Council requires adequate evidence proving safety and efficacy for all potential multisource products in the form of comparative studies using clinical or pharmacodynamic end points to demonstrate bio-equivalence.[3] These studies have to be submitted with each application for registration. Bio-equivalence focuses on the equivalence of release of the active pharmaceutical ingredient from the pharmaceutical product and its subsequent absorption into the systemic circulation.[2] In bio-equivalence studies, the molar equivalent dose of the multisource and comparator product must be used. Applicants may also request a waiver of *in vivo* bio-equivalence studies if the dissolution profile of a solid oral dosage form in three different media is conducted to prove similarity.[2]

South Africa has elements of both a developed and an emerging market economy. From a developed first world perspective it could be argued that it has a sophisticated pharmaceutical market industry mainly centered on the production and manufacture of world class generic medication. Unfortunately the registering and manufacturing of medicines is not enough because they also need to be accessible to patients.

In terms of the overall health of its population, South Africa is currently considered to be suffering a double burden of communicable and non-communicable diseases. South Africa alone had nearly 3.4 million people on antiretroviral therapy at the end of 2015, more than any other country in the world.[4] The only way that the state can afford this is through the utilization of generic medication. South Africa's legal framework that covers access to more affordable medicines consists of three pieces of legislation: The Medicines and Related Substances Act 101 of 1965 or more commonly referred to as the Medicines Act, the Competition Act 89 of 1998 and the Patents Act 57 of 1978.

Patents are the means by which multinational companies delay generic medicines from reaching the market place thus guaranteeing market exclusivity. This ensures maximum economic financial benefits for the company therefore maximizing the profit on the drug gain because the prescribed length of time a patent usually lasts is about 25 years. This allows the innovator companies to recover the costs associated with prior research and development (R&D) and also to fund new R&D.[5] New drug entities (NDE) that are launched onto the market usually carry a premium price, mainly related to registration, marketing and R&D incurred costs. Some innovator drugs have been identified as "blockbuster" drugs and have made a huge impact on many diseases and illnesses.

Besides the Patents Act, the other two forms of intellectual property legislation include trademarks and copyright. Well-known companies like Disney® and Coca-Cola® are protected by the Trademark law which is essential but not relevant to this study. The Copyright Act is significant for new drugs that have arrived on the market within the last 50 years and have generally been protected as intellectual property by the patent law thus providing an incentive for innovative discoveries that are

essential for the future of healthcare and disease prevention. Section 15(1) of the Medicines and Related Substances Act 1965 and Regulation 9 of the General Regulations in terms of the Act require that all medicines are “accompanied by a package insert” (see 1.1). In South Africa, originator companies have alleged that there has been copyright infringement of their package inserts by generic companies.

This is a direct consequence of what could be seen to be a double bind. Generic companies do not have access to the innovator companies’ data on which the innovator package insert is based to compile their package inserts and they cannot replicate the package inserts from the innovator company because this is seen as a copyright infringement. To avoid copyright infringement, many generic manufacturers in South Africa are forced to spend an inordinate amount of time and resources to develop unique package inserts. This impasse acts to delay companies’ registration of more affordable generic medicine and this can also mean that the additional costs involved in avoiding copyright infringement are passed on to patients. The encompassing scenario indicates that the health or well-being of the general population is largely profit driven.

1.1 Labelling medicines

Accurate and reliable drug information is essential for the safe and effective use of marketed products.[6] The primary means of communicating drug information is the package insert (PI). A package insert is a printed leaflet that contains information based on regulatory guidelines for the safe and effective use of a drug. In South Africa, the labelling of medicines is governed by Regulations 8, 9 and 10 of the Medicines and Related Substance Act, 1965. These being the Labelling of medicines for human use, Package inserts for medicines for human use and the Patient information leaflet, respectively. The “Package inserts for human medicines” details the labelling requirements for medicines but is specifically related to the package insert.

The EMA (European Medicines Agency) and the Food and Drug Administration (US-FDA) are two of the agencies in the world with which MCC aligns itself.[7] Medicine approval standards in the United States are considered by many to be the most demanding in the world.[8] Labelling guidelines governed by the FDA are considered to promote correct product-use, decrease reading time and increase confidence in readers’ ability to use the information provided.[9] Similarly, the labelling requirements in South Africa also promote the safe and correct use of the medicinal product. However, when comparing requirements against FDA guidelines for medicines, there are two notable absences. These include FDA requirements such as a boxed warning. A boxed warning, commonly referred to as a “black box” warning, is the most serious type of warning to be mandated by the U.S Food and Drug Administration. They are prominently featured in the labelling of drugs to warn prescribers about serious adverse reactions or special problems. These warnings are displayed on a drug’s package insert, in the Physicians’ Desk Reference, on the FDA’s website and on websites of drug marketing companies.[10] Another marked difference is the ordering risks within the package insert. The FDA considers the ordering of risk an important factor in determining the risk profile conveyed by the text.[11]

A compliant PI should contain approved, essential, accurate and relevant information about a drug. Furthermore the PI is supposed to be written in a language that is not misleading, false or promotional. The content should be evidence-based

and may need to be updated from time to time to reflect findings of relevant new pre-clinical and clinical data that becomes available.[4]

When a generic becomes available for a branded product, all the relevant prescribing information should also be identical to the originator. However the new generic PI may not always be an exact copy of the originator.Previous research in a number of countries indicates that information contained in the PI is inadequately conveyed.[12] In a study carried out in Saudi Arabia, the authors found that there was substantial disagreement in information between the generic package inserts and the British National Formulary as well as the package inserts of the brand products marketed in Saudi Arabia.[5] In another study of non-steroidal anti-inflammatory agents marketed in Saudi Arabia, the authors showed that inserts of Saudi-marketed products generally conveyed limited and incomplete information compared to their counterparts marketed in USA.[13] In the USA, it was shown that patient information leaflets do not always fully meet the federal regulations.[14] A European study also found substantial disagreement in the materials available to prescribers and patients in different countries.[15] Another useful study from Southern India revealed that of a total of 2340 hospital admissions, 6.4 % were drug related of which 50 % were due to Adverse Drug Reactions (ADRs), with a majority being believed to be preventable.[16] This suggests that providing incomplete and potentially inaccurate prescribing information contained in both the package insert as well as the patient information leaflet can cause harmful consequences which can be life-threatening. Unfortunately this seems to be a global problem. These studies raise the question about the integrity of information presented in package inserts and undermine the status of generics and their efficacious use in treating medical conditions. Documenting the change in prescribing information between the originator and the generic is therefore the subject of this research report.

The MCC and its successor will be responsible for the careful evaluation and control of the content presented in each package insert. This process occurs during the registration process. There is also a mechanism to update the PI, and this is done during the post registration phase. Thus, PIs should be updated with the latest safety and efficacy data at regular intervals by the applicant. The data included in the PI also needs to comply with the EU and US requirements. Updated information is based on Phase IV clinical trial data, post marketing surveillance and information

from double blinded and placebo controlled studies that may not have been available on first registration.[17]

While innovator companies adhere to strict guidelines for the inclusion of information in the PI, the regulatory environment may be substantially different for generic companies. Generic companies are not required to generate data on safety and efficacy for their own particular generic (multisource interchangeable medication). Obviously without this requirement, generic companies have substantially lower, research and development costs. Without the data normally derived from Phase III clinical trials, the obvious question is, “where do the generic companies source their information to populate their PIs?”

It would be completely justifiable for the generic company to source their data from the originator PI; but the PI is actually protected by copyright law. Therefore, copyright considerations have been used to undermine access to medicines. This research project is not designed to answer the question of how the PIs of generic companies are populated, but it does set out to establish the differences between the innovator and generic PIs and consider the implications of these differences.

PIs from generic companies are flawed. PIs may be outdated and may not contain current information. As the generics are usually launched in the post marketing phase, this occurrence may partly be due to a deficiency in regulatory mechanisms in South Africa to ensure that reviewing and updating of all package inserts actually occurs in the post-registration phase.[10] The backlog and lengthy timeframes at the MCC in evaluating and approving package inserts also results in an inconsistency of information amongst the various brands of a particular medicine. This gives the perception that generics are an inferior drug or worse, or a different drug. This misconception can lead to the underutilization of generics in the market place. In accordance with South African law, if generics are registered on the grounds that they are bio-equivalent to the innovator, then there is no scientific reason available to justify the differences noted between the labelling.

Previous research conducted in other countries reveals that South Africa is not alone with respect to disparities in labelling. The Food and Drug Administration (FDA) is proposing to amend its regulations to revise and clarify procedures for application holders of an approved medicine to change the product labelling to reflect certain

types of newly acquired information in advance of the FDA's review of the change. The proposed rule would create parity among application holders with respect to labelling changes by permitting holders of abbreviated new drug applications (ANDAs) to distribute revised product labelling that differs in certain respects, on a temporary basis, from the labelling of its reference listed drug (RLD) upon submission to FDA of a "change being affected" (CBE-o) supplement.[18] The proposed rule describes the process by which information regarding a CBE-o labelling supplement submitted by a new drug application (NDA) holder or an ANDA holder would be made publically available during FDA's review of the labelling change and clarifies requirements for all ANDA holders to submit conforming labelling revisions after the FDA has taken an action on the NDA or ANDA holder's CBE-o labelling supplement.[18]

1.2 Problem Statement

There is a paucity of research that documents and identifies inconsistencies in PIs. Furthermore, none of the studies conducted internationally used a systematic textual analysis by focusing on the use of language between innovator and generic PIs. The objective of this study is to fill this information gap by means of textual analysis.

1.3 Study Aim and Objective

The aim of this study is to document and tabulate the variance of prescribing information, if any, between the innovator medicines and a number of generic equivalents.

The objective is to assess the quality and quantity of prescribing information that is currently found in PI's with specific reference to the following categories: *"Indications",* "*Recommended dosage*", "*Precautions*", "*Contra-Indication*", "*Side effects*", "*Interactions"* and *"Warnings*" presented in package inserts of innovator drugs and their generic versions.

This information could serve as an early validation study for the South African Health Product Regulatory Authority (SAHPRA) and assist new local regulators in formulating or amending policies to better regulate the content of package inserts. This in turn would aid the health care professional to make better informed decisions which would be beneficial to the end user and ultimately ensure wider use of generics.

Chapter 2: Method

2.1 The Study Sample

This study is part of a bigger study detailing a number of classes of medication and within each subsection.

Inclusion criteria for drug selection:

i) The drug is widely used in South Africa. According to a study published in the South African Medicine Journal, tricyclic antidepressants and the selective serotonin re-uptake inhibitors (SSRIs) accounted for approximately 75 % of all antidepressants prescribed, with Fluoxetine being the most frequently prescribed[19]

ii) The drug should be used to treat neuropsychiatric disorders such as those identified by WHO[20]

iii) The innovator product and at least three generic brands including clones should be registered with MCC and currently are available in South Africa. A clone is an exact copy of the originator medicine which is manufactured and marketed by the same applicant of the originator medicine. This implies that the applicant marketing the clone submits the same dossier to the Medicine Control Council which is identical in all aspects to the original application with exception of the trade name

iv) The products selected for this study must contain a package insert.

v) Only package inserts in the English language will be included.

This study analyses the PIs of the molecules; citalopram, sertraline, venlafaxine, risperidone and fluoxetine. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI). SSRI's are by far the most commonly prescribed antidepressant and have evolved from a single branded product called Prozac®, to a multitude of generics.[11] This evolution of fluoxetine has certainly improved access to this important drug. Citalopram and sertraline are also SSRI's with a mechanism of action similar to that of fluoxetine, both citalopram and sertraline are more recent additions to the off-patent and have fewer generics.

A more recent addition to the antidepressant market has been the selective serotonin and noradrenergic reuptake inhibitor, venlafaxine. This is also widely used and is thought to be superior in more melancholic depression. Finally a antipsychotic, risperidone, has also been selected as an example of a more expensive drug used for more severe psychotic illnesses.

2.2 Data collection

Local, approved package inserts of registered products of fluoxetine, sertraline, venlafaxine, citalopram and risperidone were obtained from retail and/or hospital dispensaries.

2.3 Data analysis

The methodology for this study comprises of three phases: the comparative analysis of the generic package inserts (GPI) versus the innovator package inserts (IPI), followed by a semantic analysis of two molecules of PIs lastly, an examination of the ordering principles of side effects in the IPIs and GPIs.

The design for the comparative analysis of the GPI and IPI was adapted from the methodology used in a comparative PI study completed locally.[10] A comparative table has been constructed using the following package insert headings: "*Indications*", "*Recommended Dosage*", "*Precautions*", "*Contra-Indications*", "*Side Effects*", "*Interactions*" and "*Warnings*". The text under each of these headings in the GPI was compared to the corresponding section in the IPI. The presence or absence of statements in the GPI was marked and noted as present (✓) or absent (X). Additional text found in the GPIs was included in the comparison checklist. Each checklist parameter has been counted and the total of checklist parameters for the entire package insert tallied. A scorecard of variability has been compiled for each product.

The second phase of the study comprises a semantic analysis. Semantics is the study of meaning. In Linguistics, Semantics is the study of meaning that is used for understanding human expression through language. It is important to note that language always takes place in context and meanings are shaped by discourses. There are specific language practices for specific discourse communities. Thus the

technical terms used in a medical discourse are specific and related to particular meanings. This study is framed by the work of discourse analyst Norman Fairclough who argues the extent to which language can rest upon common-sense assumptions and the way in which these common-sense assumptions are shaped by power relations.[21] A crucial point to note is that our assumptions can be influenced negatively or positively by an author's choice of words. Altering the meaning of a word which has a different etymology means that the ways in which words can be interpreted shifts. Meaning also shifts across discourse communities, and the highly specialized and dense terminology that makes up medical discourse can be misinterpreted in everyday contexts by people who are not part of the discourse. Fairclough would argue that language choices, and the organization of texts are deliberate. An analysis of texts, including texts that appear merely factual like PI's reveal interests, competing discourses and power relations. The researcher analysed the level of consistency in the words in the IPIs and GPIs by identifying omissions, insertions, contradictions as well as substitutions in order to highlight the implications of dispensing the incorrect medication. Five to seven points under the following headings: "*Indications*", "*Dosage*" and "*Directions for Use*", "*Precautions*", "*Warnings*" and "*Side Effects*" were analyzed.

The third phase of the analysis considers the ordering principles of side effects. Ordering risks within a presentation is an important factor in determining the risk profile conveyed by a package insert regardless of whether it is directed towards the health care professional or consumer.

Chapter 3: Results

3.1 A comparison between the Originator Product and their generics

The first phase of the study involved the comparative analysis of Prozac® versus three generics; one generic is actually a clone being Lilly-Fluoxetine® which is manufactured by the same parent company. The other two generics are Nuzak® and Lorien®. Another drug in the SSRI antidepressant class was citalopram where the innovator Cipramil® was compared to three generic products named Cilift®, DRL-Citalopram® and Citalohexal®. A third molecule, sertraline was included and the innovator Zoloft® was compared to three available generics on the market, these being Serlife®, Aspen Sertraline® and Serdep®. The fourth molecule included in this study is venlafaxine which is an antidepressant with dual serotonin and noradrenaline reuptake inhibitor activity which was analysed and the innovator Effexor XR® was compared to the three generics available, which are Venlor XR®, Venlafaxine XR® and Sandoz Venlafaxine XL®. Finally, a fifth molecule was chosen from the antipsychotic class. This being risperidone and the innovator Risperdal® was analysed and compared to DRL-Risperidone®, Rispercor® and Risperlet® which is also a clone. Tables 1 to 5 display the comparison between the information in the originator product and that found in the generic package inserts for fluoxetine, citalopram, sertraline, risperidone and venlafaxine .

Table 1: Reference Checklist 1- Items for Assessing Agreement of Drug Information for fluoxetine. A Comparative Analysis between Prozac® & it's Generics

PRODUCT	PROZAC® (ORIGINATOR)	Lilly-fluoxetine®	Nuzak®	Lorien®
1.Indications				
Major Depressive Disorder	✓	✓	✓	✓
Obsessive Compulsive Disorder	✓	✓	✓	✓
Bulimia Nervosa	✓	✓	✓	✓
2. Recommended dosage adults in oral dosage form				
Major depressive disorder -20mg per day, in the morning,	✓	✓	✓	✓
Obsessive Compulsive Disorder- 20 -60mg per day	✓	✓	✓	✓
Bulimia Nervosa- 60mg per day	✓	✓	✓	✓
The recommended dose may be increased or decreased	✓	✓	X	X
Doses above 80 mg/day are not recommended for any indication	✓	✓	X	X
Dosages over 20 mg per day are not recommended in the elderly	✓	✓	X	X
3.Precautions				
Introduced cautiously in patients with a history of seizures	✓	✓	✓	X
Discontinue if patients develop seizures	✓	✓	X	✓
Avoided in patients with unstable epilepsy or monitored if they have epilepsy	✓	✓	✓	✓
Caution in acute cardiac disease	✓	✓	✓	✓
Loss of mass which could be undesirable in under mass patients	✓	✓	✓	✓
In diabetic patients it may alter glycaemic control, hypoglycaemia during treatment and hyperglycaemia after discontinuation	✓	✓	✓	✓
Altered platelet function or abnormal laboratory results	✓	✓	✓	✓
Impairs judgement, thinking or motor skills	✓	✓	✓	✓
Risk of suicide	✓	✓	X	✓
Extra pyramidal symptoms and aggravates Parkinson's disease	✓	✓	X	X
Discontinuation leads to withdrawal symptoms, including paraesthesia, dizziness, headache, insomnia, tremor, confusion, sensory disturbances, agitation, anxiety and nausea	✓	✓	X	X
Caution in elderly	X	X	✓	X
Patients or those taking multiple central nervous system-active medications	X	X	✓	X
Safety and efficacy in children has not been established	X	X	✓	X
Do not use in pregnancy and lactation	X	X	✓	X
Narrow angle glaucoma may be aggravated	X	X	✓	X
Withdraw if allergic skin reaction appears	X	X	✓	X

PRODUCT	PROZAC® (ORIGINATOR)	Lilly-fluoxetine®	Nuzak®	Lorien®
4.Contra-Indications				
Patient known to be hypersensitive to any ingredient	✓	✓	✓	✓
Use of Monoamine oxidase inhibitors (MAOI'S) during therapy or within 14 days MAOI'S	✓	✓	✓	✓
Thioridazine should not be administered with Prozac or within a minimum of 5 weeks after Prozac® has been discontinued	✓	✓	X	X
Pediatric use: safety and efficacy has not been established	✓	✓	✓	✓
Severe renal failure (glomerular filtration of less than 10 ml per minute)	X	X	✓	✓
In acute phase of myocardial infarction	X	X	✓	X
Unstable epilepsy	X	X	✓	X
Safety in pregnancy and lactation has not been established	X	X	✓	✓
5. Side effects				
Chest pain, chills	✓	✓	X	X
Headache	✓	✓	✓	✓
Asthenia	✓	✓	✓	✓
Flu syndrome	✓	✓	✓	✓
Fever	✓	✓	✓	✓
Vasodilation	✓	✓	✓	✓
Nausea	✓	✓	✓	✓
Diarrhea	✓	✓	✓	✓
Anorexia	X	X	✓	✓
Dry mouth	✓	✓	✓	✓
Loss of appetite	X	X	✓	✓
Dyspepsia	✓	✓	✓	✓
Constipation	✓	✓	✓	✓
Flatulence	✓	✓	✓	✓
Vomiting	✓	✓	✓	✓
Loss of mass	✓	✓	✓	✓
Insomnia	✓	✓	✓	✓
Nervousness	✓	✓	✓	✓
Anxiety	✓	✓	✓	✓

PRODUCT	PROZAC® (ORIGINATOR)	Lilly-fluoxetine®	Nuzak®	Lorien®
5.Side effects (Cont.)				
Somnolence	✓	✓	✓	✓
Dizziness	✓	✓	✓	✓
Tremor	✓	✓	✓	✓
Libido decreased	X	X	✓	✓
Libido increased	✓	✓	X	X
Thinking abnormal	✓	✓	X	✓
Hypomania or mania	✓	✓	✓	✓
Suicidal ideation	✓	✓	✓	✓
Hypernatremia	✓	✓	✓	✓
Sexual dysfunction (delayed or inhibited)	✓	✓	✓	✓
Elevated serum transaminase	✓	✓	✓	✓
Cerebral vascular accident	✓	✓	✓	✓
Confusion	✓	✓	✓	✓
Ecchymosis	✓	✓	✓	✓
Eosinophillic pneumonia	✓	✓	✓	✓
Hyperprolactaemia	✓	✓	✓	✓
Pancreatitis	✓	✓	✓	✓
Vaginal bleeding after withdrawal of medication	✓	✓	✓	✓
Violent behavior	✓	✓	✓	✓
Asthma	✓	✓	✓	✓
Epistaxis	✓	✓	✓	✓
Hiccup	✓	✓	✓	✓
Hyperventilation	✓	✓	✓	✓
Hypothyroidism	✓	✓	✓	✓
Diabetic acidosis	✓	✓	✓	✓
Anaemia	✓	✓	✓	✓
Urinary frequency	✓	✓	✓	✓
Sweating	✓	✓	✓	✓
Rash	✓	✓	✓	✓

PRODUCT	PROZAC® (ORIGINATOR)	Lilly-fluoxetine®	Nuzak®	Lorien®
5.Side effects (Cont.)				
Acute abnormal syndrome, hypothermia, intentional injury, photosensitivity reaction	✓	✓	X	X
Haemorrhage, hypertension, palpitation	✓	✓	X	X
Angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache	✓	✓	X	X
Atrial fibrillation, bradycardia, cerebral embolism, cerebral ischaemia, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation	✓	✓	X	X
Increased appetite	✓	✓	X	X
Aphthous stomatitis, cholelithiasis, colitis, dysphagia, eruction, oesophagitis, gastritis,gastroenteritis. Glossitis, gum haemorrhage, hyperchorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, stomach ulcer, stomatitis, thirst	✓	✓	X	X
Biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, oesophageal ulcer, faecal incontinence, gastrointestinal haemorrhage , hematemesis, haemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal haemorrhage, salivary gland enlargement, stomach ulcer haemorrhage, tongue oedema.	✓	✓	X	X
Diabetic mellitus	✓	✓	X	X
Blood dyscrasia, hypochromic anaemia, leucopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythaemia, thrombocytopenia	✓	✓	X	X
Weight gain	✓	✓	X	X
Dehydration, generalized oedema, gout, hypercholesteraemia, hyperlipaemia, hypokalaemia, peripheral oedema	✓	✓	X	X
Alcohol intolerance, alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, hyperkalaemia, hyperuricaemia, hypocalcaemia, iron deficiency anemia, ALT increased.	✓	✓	X	X
Arthritis, bone pain, bursitis, leg cramps, tenosynovitis	✓	✓	X	X
Arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis	✓	✓	X	X
Agitation, amnesia, emotional lability, sleep disorder	✓	✓	X	X
Abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder, psychosis, vertigo	✓	✓	X	X
Abnormal electroencephalogram, antisocial reaction, circumoralparaesthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperaesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.	✓	✓	X	X
Apnoea, atelectasis, cough decreased, emphysema, haemoptysis, hypoventilation, hypoxia, larynx oedema, lung oedema, pneumothorax, stidor	✓	✓	X	X
Acne, contact dermatitis, eczema, maculopapular rash, skin discolouration, skin ulcer, vesiculobullous rash	✓	✓	X	X

PRODUCT	PROZAC® (ORIGINATOR)	Lilly-fluoxetine®	Nuzak®	Lorien®
5.Side effects (Cont.)				
Puritis	✓	✓	X	X
Ear pain	✓	✓	✓	✓
Conjunctivitis	✓	✓	✓	✓
Priaprism	✓	✓	✓	✓
Abnormal vision	✓	✓	✓	✓
Neuroleptic malignant syndrome	✓	✓	✓	✓
Face oedema, malaise, pelvic pain	✓	✓	X	X
Furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea	✓	✓	X	X
Taste perversion, tinnitus	✓	✓	X	X
Dry eyes, mydriasis, photophobia	✓	✓	X	X
Blepharitis, deafness, diplopia, exophthalmos, eye haemorrhage, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect	✓	✓	X	X
Abortion, albuminuria, amenorrhoea, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation, fibrocystic breast, haematuria, leucorrhoea, menorrhagia, metrorrhagia, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal haemorrhage	✓	✓	X	X
Breast engorgement, glycosuria, hypomenorrhoea, kidney pain, oliguria, uterine haemorrhage, uterine fibroids enlarged	✓	✓	X	X
6. Interaction				
Medications metabolized by cytochrome P450IID6 isoenzyme	✓	✓	✓	✓
Concomitant use with other monoamine oxidase inhibitors	✓	✓	✓	✓
Concomitant use with other serotogernic activity	✓	✓	✓	✓
There is a 2-fold increase in other antidepressants blood levels	✓	✓	✓	✓
CNS active drugs e.g. lithium levels are increased or decreased	✓	✓	✓	✓
Reaction increases with tryptophan (agitation, restlessness and gastro-intestinal distress)	✓	✓	✓	✓
Plasma binding of fluoxetine may be altered by other agents	✓	✓	✓	✓
Long elimination half-life of fluoxetine and its metabolites with regards to pharmacokinetics, pharmacodynamics drug interaction	✓	✓	✓	✓
Plasma concentration altered of other plasma protein bound drugs e.g. warfarin, digoxin	✓	✓	✓	✓
7. Warnings				
Worsening of their depression and/or emergence suicidal ideation	✓	✓	X	X
Serotonin syndrome	✓	✓	X	X
Rash and possibly allergic reactions	✓	✓	✓	✓
This medicine must be kept out of reach of children. Even a small dose may be fatal	X	X	✓	X

Table 2: Reference Checklist 2 - Items for Assessing Agreement of Drug Information for citalopram. A Comparative Analysis between Cipramil® & it's Generics

PRODUCT	Cipramil® (ORIGINATOR)	Cilift®	DRL-Citalopram®	Citalohexal®
1.Indications				
Depression	✓	✓	✓	✓
Panic disorder with or without agoraphobia	✓	✓	✓	✓
Obsessive-compulsive disorder	✓	X	✓	✓
2. Recommended dosage				
adults in oral dosage form *In the treatment of depression:* the dose of 20 to 60 mg daily as a single oral dose may be taken in the morning or the evening not necessarily with food	✓	✓	✓	✓
In the treatment of panic disorder with or without agoraphobia: The initial dose is 10 mg daily by mouth, increasing to 20 mg daily once a week. The dose may be increased thereafter as required up to a maximum of 60 mg	✓	✓	✓	✓
Obsessive compulsive disorder: Initially 20 mg per day as a single dose. This dose can be increased by 20 mg increments to a maximum of 60 mg per day depending on the patient's response.	✓	X	✓	✓
Children up to 18 years of age: Not recommended, as safety and efficacy have not been established	X	✓	X	X
Reduced hepatic function: Dosage should be halved	✓	✓	✓	✓
Reduced renal function: Dosage adjustment is not necessary in cases of mild or moderate renal impairment.	✓	✓	✓	✓
Note: it should be withdrawn gradually to reduce the risk of withdrawal symptoms.	✓	✓	✓	✓
3. Precautions				
Patients should be closely monitored during early therapy as suicide is an inherent risk in depressed patients	**Precautions included with Side effects**	✓	✓	✓
Should be used with caution in patients with epilepsy or a history of such disorders (and should be avoided if the epilepsy is poorly controlled)		✓	X	✓
Impairment of performance of skilled tasks. If affected these patients should not operate machinery or drive.		X	✓	X
Serotonin syndrome is more likely to occur after an increase in dose.		X	✓	X
Avoid alcohol		X	✓	X
Safety and efficacy in children under 18 years of age have not been established		X	✓	X
If therapy is discontinued, it is recommended that the dose is decreased gradually in order to prevent the possibility of a withdrawal syndrome.		X	X	✓

PRODUCT	Cipramil® (ORIGINATOR)	Cilift®	DRL-Citalopram®	Citalohexal®
4.Contra-Indications				
Hypersensitivity	✓	✓	✓	✓
Severe hepatic or renal failure (creatinine clearance of less than 20 ml/min)	✓	✓	✓	✓
Safety in pregnancy and lactation has not been established	✓	✓	✓	✓
Concurrent use with a monoamine oxidase inhibitor (MAOI). At least 14 days should elapse between discontinuing the MAOI and initiating therapy with CITALOPRAM. MAOIs should not be introduced for 7 days after discontinuation of CITALOPRAM	X	X	✓	✓
Children up to 18 years of age, not recommended, as safety and efficacy have not been established	X	X	✓	✓
5. Side Effects				
General: Headache	✓	✓	✓	✓
Sweating	✓	✓	✓	✓
Fatigue	✓	✓	✓	✓
Tremor	✓	✓	✓	✓
Weight loss / weight gain	✓	✓	✓	✓
Dizziness	✓	✓	✓	✓
Cardiovascular: Palpitations	✓	✓	✓	✓
A decrease in pulse rate has been reported	✓	✓	✓	✓
Central nervous system: Anxiety	✓	✓	✓	✓
Restlessness	✓	✓	✓	✓
Nervousness	✓	✓	✓	✓
Insomnia	✓	✓	✓	✓
Somnolence	✓	✓	✓	✓
Drowsiness and paraesthesia	✓	✓	✓	✓
Gastro-intestinal: Dry mouth	✓	✓	✓	✓
Nausea	✓	✓	✓	✓
Vomiting	✓	✓	✓	✓
Dyspepsia	✓	✓	✓	✓
Constipation/diarrhea	✓	✓	✓	✓

PRODUCT	Cipramil® (ORIGINATOR)	Cilift®	DRL-Citalopram®	Citalohexal®
5.Side effects (Cont.)				
Urogenital: Micturition disorder	✓	✓	✓	✓
Eyes: Accomodation disturbances	✓	✓	✓	✓
Less common: Malaise	✓	✓	✓	✓
Yawning	✓	✓	✓	✓
Convulsions	✓	✓	✓	✓
Extrapyramidal side effects	✓	✓	✓	✓
Agitation	✓	✓	✓	✓
Confusion	✓	✓	✓	✓
Impaired concentration	✓	✓	✓	✓
Sexual dysfunction (decreased libido, ejaculation disorder)	✓	✓	✓	✓
Mania	✓	✓	✓	✓
Salivation	✓	✓	✓	✓
Pruritus' or skin rashes	✓	✓	✓	✓
Nasal congestion	✓	✓	✓	✓
Mydriasis	X	✓	X	X
Hyponatremia (particularly in the elderly)	✓	✓	✓	✓
Very rare: Hepatitis, serotonin syndrome, neuroleptic malignant syndrome	✓	X	✓	✓
Hostility, suicidal ideation and self-harm have been reported in children	X	X	X	✓
Asthenia	✓	X	✓	✓
6. Interaction				
Simultaneous administration of MAOI's	✓	✓	✓	✓
Concomitant administration with other antidepressant therapy may result in severe adverse reactions "Serotonin syndrome". At least one week should elapse between withdrawing an SSRI and starting any medicine liable to provoke a serious reaction (e.g. phenelzine).	X	✓	✓	✓
Interacts with imipramine, moclobemide, selegeline and sumatriptan	✓	✓	✓	✓
Alcohol – The effects of alcohol may be increased	X	X	✓	X
Warfarin - The anticoagulant activity of warfarin may be increased	X	X	✓	X
Cimetidine – The AUC and the maximum plasma concentration of CITALOPRAM are increased when CITALOPRAM is administered concurrently with cimetidine	X	X	✓	X

PRODUCT	Cipramil® (ORIGINATOR)	Cilift®	DRL-Citalopram®	Citalohexal®
7.Warnings				
Should not be given to patients receiving Monoamine Oxidase Inhibitors (MAO's) or for at least 14 days after their discontinuation	✓	✓	✓	X
MAOI's should not be introduced for seven days after discontinuing Citalopram	✓	✓	✓	X
If the patient enters a manic state, must discontinue.	✓	✓	✓	✓
Impairment of performance of skilled tasks and, if affected, patients should not drive or operate heavy machinery.	✓	✓	✓	✓
Use in the elderly- The half-life is increased and clearance decreased due to a reduced rate of metabolism. A lower dose is recommended in the elderly	X	✓	X	X
Use in impaired hepatic function- Clearance of DRL CITALOPRAM is reduced. Cautious dosage titration and a lower maximum dose are recommended	X	X	✓	X
Use in renal impairment – Elimination is decreased. If creatinine clearance is less than 20 ml/min, CITALOPRAM should not be used	X	X	✓	X
Other serotonergic medicines or medicines with serotonergic activity- Increased risk of developing serotonin syndrome, a rare but potentially fatal hyperserotonergic state	X	X	✓	X
Use in seizures or history thereof - There is an increased risk of seizures. And be used with caution in patients with controlled epilepsy and avoided in patients who are poorly controlled epileptics. Care is advised in patients receiving electroconvulsive therapy.	X	X	✓	X
Use in pre-existing slow heart rates CITALOPRAM may cause a reduction in heart rate. Caution is advised in patients with pre-existing slow heart rates.	X	X	✓	X
Diabetes mellitus – Rare occurrences of hypoglycaemia have been reported	X	X	✓	X
Use with other medicines- moclobemide, alcohol, warfarin and cimetidine	X	X	✓	X
Suicidal ideation	X	X	✓	✓

Table 3: Reference Checklist 3 - Items for Assessing Agreement of Drug Information for Sertraline. A Comparative Analysis between Zoloft® & it's Generics

PRODUCT	ZOLOFT® (ORIGINATOR)	SERLIFE®	ASPEN SETRA LINE®	SERDE P®
1.Indications				
Major depressive disorder	✓	✓	✓	✓
Obsessive compulsive disorder	✓	✓	✓	✓
Panic disorder	✓	X	✓	✓
Obsessive compulsive disorder in children between 13-17 years	✓	X	X	X
2. Recommended				
Dosage: adults in oral dosage *Major depression* 50 mg daily initially, may be increased up by 50 mg increments over a period of 2 weeks to a maximum of 200 mg daily.	✓	✓	✓	✓
Obsessive compulsive disorder: 50 mg daily, if increased above 100 mg daily it has no additional benefit	✓	✓	✓	✓
Panic disorder: 25 mg daily initially can be increased to 50 mg daily after 1 week	✓	X	✓	✓
Obsessive compulsive disorder for children between 13-17 years : 50 mg initially and may be increased up to 200 mg after 1 week	✓	X	X	X
3. Precautions				
Activation of hypomania/mania	✓	X	X	X
Significant weight loss	✓	X	X	X
Discontinue if seizures develop	✓	X	X	X
Epilepsy	✓	X	X	X
Suicide ideation	✓	X	X	X
Protein bound medicines	✓	X	X	X
Co-administration of SERTRALINE with other agents which enhance serotonergic neurotransmission, such as tryptophan or fenfluramine, should be avoided due to the potential for pharmacodynamics interaction.	✓	✓	✓	✓
Switching from other antidepressants or anti obsessional agents	✓	X	✓	X
Other interactions- Co-administration with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters	✓	X	X	X
Co-administration with cimetidine caused a substantial decrease in SERTRALINE clearance	✓	X	X	X
Warfarin-Co-administration of SERTRALINE 200 mg daily and warfarin resulted in a small but statistically significant increase in prothrombin time.	✓	X	X	X
Lithium- It is recommended that plasma lithium levels be monitored following initiation of SERTRALINE therapy, so that appropriate adjustments to the lithium dose may be made if necessary	✓	X	X	X
Medicines metabolized by cytochrome P450 (CYP) 2D6	✓	X	X	X

PRODUCT	ZOLOFT® (ORIGINATOR)	SERLIFE®	ASPEN SETRA LINE®	SERDE P®
3. Precautions (cont.)				
History of recent myocardial infarction or unstable heart disease	✓	X	X	X
Liver impairment	✓	X	X	X
Abrupt discontinuation	✓	X	X	X
Weal uricosuric effect- associated with a mean decrease in serum uric acid of approximately 7 %	✓	X	X	X
Electroconvulsive therapy (ECT) -There are no clinical studies establishing the risks or benefits of combined use of ECT and SERTRALINE	✓	✓	✓	✓
Hyponatraemia	X	✓	✓	✓
Asymptomatic elevations of serum transaminases	X	✓	✓	✓
Altered platelet function	X	✓	✓	✓
Aggravation of Parkinson's disease	X	✓	✓	✓
4. Contra-Indications				
Using MAOI	✓	✓	✓	✓
Pregnancy and lactation	✓	✓	X	X
Concomitant use with pimozide	✓	X	X	✓
Hepatic or renal insufficiency	✓	X	✓	✓
Children < 18 years for OCD and major depression	✓	X	X	✓
Hypersensitivity	X	✓	✓	✓
5. Side – Effects				
Gastro-intestinal disorders: *Frequent:* Anorexia	✓	✓	✓	✓
Nausea	✓	✓	✓	✓
Diarrhea /loose stools	✓	✓	✓	✓
Dyspepsia	✓	✓	✓	✓
Abdominal pain	✓	✓	✓	✓
Dry mouth	✓	✓	✓	✓
Flatulence	✓	✓	✓	✓
Less frequent: Constipation	✓	✓	✓	✓
Vomiting	✓	✓	✓	✓
Increased appetite	✓	✓	✓	✓
Taste perversion	✓	✓	✓	✓

PRODUCT	ZOLOFT® (ORIGINATOR)	SERLIFE®	ASPEN SETRA LINE®	SERDE P®
5. Side-effects (Cont.)				
Central nervous system disorders: *Frequent:* Tremor	✓	✓	✓	✓
Dizziness	✓	✓	✓	✓
Insomnia	✓	✓	✓	✓
Somnolence	✓	✓	✓	✓
Fatigue	✓	✓	✓	✓
Sexual dysfunction (primarily ejaculatory delay in males)	✓	✓	✓	✓
Headache	✓	✓	✓	✓
Less Frequent: Agitation	✓	✓	✓	✓
Nervousness	✓	✓	✓	✓
Anxiety	✓	✓	✓	✓
Yawning	✓	✓	✓	✓
Paresthesia	✓	✓	✓	✓
Hypoesthesia	✓	✓	✓	✓
Twitching	✓	✓	✓	✓
Hypertonia	✓	✓	✓	✓
Female sexual dysfunction	✓	✓	✓	✓
Impaired concentration	✓	X	✓	✓
Psychosis	✓	✓	✓	✓
Tinnitus	✓	X	✓	✓
Convulsions	✓	X	✓	✓
Movement disorder (such as gait abnormalities)	✓	X	✓	✓
Cardiac disorders: *Less frequent:* Palpitations	✓	✓	✓	✓
Skin and subcutaneous tissue disorders: *Less frequent:* Rash	✓	✓	✓	✓
Hot flushes	✓	✓	✓	✓

PRODUCT	ZOLOFT® (ORIGINATOR)	SERLIFE®	ASPEN SETRA LINE®	SERDE P®
5. Side-effects (Cont.)				
Erythema multiform	✓	X	✓	✓
Metabolic and nutritional disorders: Thirst	✓	✓	✓	✓
Eye disorders: *Less frequent:* Vision abnormal	✓	✓	✓	✓
Respiratory disorders: Rhinitis	✓	✓	✓	✓
Pharyngitis	✓	✓	✓	✓
Renal and urinary disorders: Micturition frequency	✓	✓	✓	✓
Micturition disorder	✓	✓	✓	✓
Musculo-skeletal disorders: Myalgia	✓	✓	✓	✓
Hepatobiliary disorders: Pancreatitis	✓	X	✓	✓
Serious liver events (including hepatitis, jaundice and liver failure)	✓	X	✓	✓
Reproductive system and breast disorders: *Less frequent:* Galactorrhoea	✓	X	✓	✓
Hyperprolactinaemia	✓	X	✓	✓
Menstrual symptoms	✓	✓	✓	✓
General disorders: *Frequent:* Increased sweating	✓	✓	✓	✓
Less frequent: Fever	✓	✓	✓	✓
Back pain	✓	✓	✓	✓
6. Interaction				
Concomitant use of alcohol is not recommended	✓	✓	✓	✓
Small but statistically significant changes in some pharmacokinetic parameters of diazepam and tolbutamide have been observed when these medicines were co-administered	✓	✓	✓	✓
The clearance of it is significantly decreased by cimetidine. However, its clinical significance is unknown	✓	✓	✓	✓
Prothrombin time should be monitored in patients receiving warfarin concomitantly, since a statistically significant increase in prothrombin time has been observed in such patients	✓	✓	✓	✓

PRODUCT	ZOLOFT® (ORIGINATOR)	SERLIFE®	ASPEN SETRA LINE®	SERDE P®
6. Interaction (Cont.)				
The SSRIs have been reported to interact with medicines metabolized by cytochrome P450.	✓	✓	✓	✓
The pharmacokinetics of lithium are not altered, however, a careful monitoring of plasma lithium concentration is recommended for making adjustments in lithium doses	✓	✓	✓	✓
With MAOI	X	X	✓	✓
Plasma protein bound drugs	✓	X	✓	✓
Seizures	✓	✓	✓	✓
Avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored.	✓	✓	✓	✓
Should be discontinued in any patient who develops seizures	✓	✓	✓	✓
The possibility of a suicide attempt	✓	✓	✓	✓
Weak uricosuric effect –associated with a mean decrease in serum uric acid of approximately 7 %	✓	✓	✓	✓
Electroconvulsive therapy (ECT) -There are no clinical studies establishing the risks or benefits of combined use of ECT and SERTRALINE	✓	✓	✓	✓
Driving/Use of machinery, patients should be cautioned accordingly when driving a car or operating machinery	✓	✓	✓	✓
Use in patients with concomitant illness-Caution is advisable in using in patients with diseases or conditions that could affect metabolism or hemodynamic responses	✓	✓	✓	✓
Patients with a recent history of myocardial infarction or unstable heart disease	✓	✓	✓	✓
Liver impairment	✓	✓	✓	✓
Renal impairment	✓	✓	✓	✓
Interference with cognitive and motor performance	✓	✓	✓	✓
7. Warnings				
Activation of mania or hypomania	✓	✓	✓	✓
Weight loss	✓	✓	✓	✓
Seizures	✓	✓	✓	✓
Avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored	✓	✓	✓	✓
Should be discontinued in any patient who develops seizures	✓	✓	✓	✓
The possibility of a suicide attempt	✓	✓	✓	✓
Weak uricosuric effect-associated with mean decrease in serum uric acid of approximately 7%	✓	X	✓	✓

PRODUCT	ZOLOFT® (ORIGINATOR)	SERLIFE®	ASPEN SETRA LINE®	SERDE P®
7. Warnings (Cont.)				
Electroconvulsive therapy (ECT) -There are no clinical studies establishing the risks or benefits of combined use of ECT and SERTRALINE	✓	✓	✓	✓
Driving/Use of machinery, patients should be cautioned accordingly when driving a car or operating machinery	✓	✓	✓	✓
Use in patients with concomitant illness-Caution is advisable in using in patients with diseases or conditions that could affect metabolism or hemodynamic responses	✓	✓	✓	✓
Patients with a recent history of myocardial infarction or unstable heart disease	✓	✓	✓	✓
Liver impairment	✓	✓	✓	✓
Renal impairment	✓	✓	✓	✓
Interference with cognitive and motor performance	✓	✓	✓	✓
Use with MAOI	✓	✓	X	X
Concomitant use with alcohol	✓	✓	X	X

Table 4: Reference Checklist 4 - Items for Assessing Agreement of Drug Information for risperidone. A Comparative Analysis between Risperdal® & it's Generics

PRODUCT	RISPERDAL® (ORIGINATOR)	DRL-RISPERIDONE®	RISPACOR®	RISPERLET®
1.Indications				
Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms and/or the negative symptoms	✓	✓	✓	✓
Behavioral disturbances in patients with dementia in whom symptoms such as aggressiveness (verbal outbursts, physical violence), activity disturbances (agitation, wandering) or psychotic symptoms are prominent	✓	✓	✓	✓
Conduct and other disruptive behavior disorders in children (aged 5-12 years), with sub average intellectual functioning or mental retardation in whom destructive behaviors (e.g. aggression, impulsivity and self-injurious behaviors) are prominent	✓	✓	✓	✓
2. Recommended Dosage				
Schizophrenia Adults: Given once or twice daily. Patients should start with 2 mg/day and may be increased on the second day to 4 mg/day. From then on, the dosage can be maintained unchanged, or further individualized, if needed. Doses above 6 mg/day (when administered twice daily) were associated with more extrapyramidal symptoms and other	✓	✓	✓	✓
Adverse effects and are not generally recommended	✓	✓	✓	✓
Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause an increased incidence of side-effects such as extrapyramidal symptoms	✓	✓	✓	✓
Dosages above 10 mg/day should only be considered if the benefits outweighs the risk	✓	✓	✓	✓
The maximum total daily dose is 16 mg/day. A benzodiazepine may be added to RISPERIDONE if additional sedation is required	✓	✓	✓	✓
Renal- and liver- diseased patients: Caution should be exercised with these groups of patients. It is recommended to halve both the starting dose and subsequent dose increments	✓	✓	✓	✓
Elderly patients: A starting dose of 0.5 mg b.i.d is recommended. This dosage can be individually adjusted with 0.5 mg b.i.d increments to 1-2 mg b.i.d.	✓	✓	✓	✓
Children: Not for children under 15 years as efficacy and safety in children under the age of 15 years have not been demonstrated in schizophrenia	✓	✓	✓	✓
Behavioral disturbances in patients with dementia: A starting dose of 0.25 mg b.i.d is recommended. This dosage can be individually adjusted by increments of 0.25 mg b.i.d, not more frequently than every other day, if needed. The optimum dose is 0, 5 mg b.i.d for most patients. Some patients, however, may benefit from doses up to 1 mg b.i.d. Once patients have reached their target dose, once –daily dosing regimen can be considered	✓	✓	✓	✓
Conduct and other disruptive behavior disorders in children 5-12 years of age: Subjects <50 kg: A starting dose of 0, 01 mg/kg once daily is recommended. This dosage can be individually adjusted by increments of 0, 01 mg/kg once daily not more frequently than every other day, if needed. The recommended maintenance dose is 0, 02 – 0, 04 mg/kg once daily. The mean dose is 0, 03 mg/kg once daily. The continued use of RISPERDAL must be evaluated and justified on an ongoing basis. Experience is lacking in children aged less than 5 years	✓	✓	✓	✓

PRODUCT	RISPERDAL® (ORIGINATOR)	DRL-RISPERIDONE®	RISPACOR®	RISPERLET®
3. Precautions				
May impair mental alertness. Patients should be advised not to drive or operate machinery until their individual susceptibility is known	✓	✓	✓	✓
It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and patients with renal or liver insufficiency	✓	✓	✓	✓
Used with caution in patients with known cardiovascular disease, and the dosage should be gradually titrated as recommended	✓	✓	✓	✓
A dose reduction should be considered if hypotension occurs	✓	✓	✓	✓
Caution should be used when prescribing to patients with Parkinson disease	✓	✓	✓	✓
Patients may be advised to refrain from excessive eating in view of the possibility of weight gain	✓	✓	✓	✓
Tardive dyskinesia. Potentially irreversible	X	✓	✓	✓
Neuroleptic malignant syndrome	X	✓	✓	✓
Concomitant use with furosemide: higher mortality in patients treated with furosemide and risperidone	X	✓	✓	✓
Alpha-blocking activity due to the alpha-blocking activity of RISPERIDONE (orthostatic) hypotension can occur, especially during the initial dose-titration period	X	✓	✓	✓
Galactose intolerance	X	X	✓	✓
4. Contra-Indication				
Known sensitivity to the medicine	✓	✓	✓	✓
Safety in pregnancy or lactating women has not been established. Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving RISPERIDONE should not breast feed.	✓	✓	X	X
Conduct and behavior disorders children: Not for children under 5 years as efficacy and safety in children under the age of 5 years have not been demonstrated.	✓	✓	✓	✓
5. Side Effects				
Insomnia	✓	✓	✓	✓
Agitation	✓	✓	✓	✓
Extrapyramidal disorder	✓	✓	✓	✓
Anxiety	✓	✓	✓	✓
Headache	✓	✓	✓	✓
Sedation has been reported more frequently in children and adolescents than in adults	✓	✓	✓	✓
Less commonly observed are: Somnolence	✓	✓	✓	✓
Fatigue	✓	✓	✓	✓
Dizziness	✓	✓	✓	✓

PRODUCT	RISPERDAL® (ORIGINATOR)	DRL-RISPERIDONE®	RISPACOR®	RISPERLET®
5. Side Effects (Cont.)				
Impaired concentration	✓	✓	✓	✓
Constipation	✓	✓	✓	✓
Dyspepsia	✓	✓	✓	✓
Nausea	✓	✓	✓	✓
Vomiting	✓	✓	✓	✓
Abdominal pain	✓	✓	✓	✓
Weight gain	✓	✓	✓	✓
Blurred vision	✓	✓	✓	✓
Priapism, erectile dysfunction, ejaculatory dysfunction, orgiastic dysfunction	✓	✓	✓	✓
Urinary incontinence	✓	✓	✓	✓
Rhinitis	✓	✓	✓	✓
Rash and other allergic reactions have been observed	✓	✓	✓	✓
The following dose dependent extrapyramidal symptoms have been observed: Tremor	✓	✓	✓	✓
Rigidity	✓	✓	✓	✓
Hyper salivation	✓	✓	✓	✓
Bradykinesia	✓	✓	✓	✓
Oculogyric crisis	✓	✓	✓	✓
Akathisia (Hyperkinesia) and acute dystonia	✓	✓	✓	✓
Hypokinesia	✓	✓	✓	✓
Tardive dyskinesia (TD)	✓	✓	✓	✓
Neuroleptic malignant syndrome (NMS) should include 1. Immediate discontinuation of all antipsychotic medicines and other drugs not essential to concurrent therapy; 2. 2. Intensive symptomatic treatment and medical monitoring; and 3. Treatment of any concomitant serious medical problems for which specific treatments are available.	✓	✓	✓	✓
Caution is recommended when treating patients with epilepsy (Orthostatic) hypotension and (reflex) tachycardia or hypertension has been observed.	✓	✓	✓	✓

PRODUCT	RISPERDAL® (ORIGINATOR)	DRL-RISPERIDONE®	RISPACOR®	RISPERLET®
5. Side Effects (Cont.)				
A mild fall in neutrophil and/or thrombocytes count has been reported.	✓	✓	✓	✓
RIOSPERDAL can induce a dose-dependent increase in plasma prolactin: Galactorrhoea	✓	✓	✓	✓
Gynaecomastia, disturbances of the menstrual cycle and amenorrhoea	✓	✓	✓	✓
Cerebrovascular accidents have been observed during treatment with risperidone	✓	✓	✓	✓
Water intoxication, either due to polydipsia or the syndrome of inappropriate	✓	✓	✓	✓
Secretion of the antidiuretic hormone (SIADH)	✓	✓	✓	✓
Body temperature dysregulation, have been reported	✓	✓	✓	✓
6. Interaction				
Used with caution in combination with alcohol and other centrally acting medicines	✓	✓	X	X
It may antagonize the effect of levodopa and other dopamine agonists	✓	✓	✓	✓
Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of RISPERIDONE. Similar effects may be observed with other hepatic enzyme inducers	✓	✓	✓	✓
Phenothiazine's, tricyclic antidepressants and some beta-blockers may increase the plasma concentration of risperidone but not that of the antipsychotic fraction	✓	✓	✓	✓
Fluoxetine may increase the plasma concentration of risperidone but less so of the anti-psychotic fraction	✓	✓	✓	✓
When taken together with other highly protein-bound medicines (e.g. diazepam, warfarin, digoxin, imipramine and propranolol), there is no clinically relevant displacement of either agent from the plasma proteins	✓	✓	✓	✓
Valproate T_{max}increased from 1,3 hours to 2,0 hours.	✓	✓	✓	✓
Topiramate Modest decrease in risperidone bioavailability but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance	X	✓	✓	✓
Quetiapine: No significant interaction	X	✓	✓	✓
Clozapine: No significant interaction	✓	✓	✓	✓
Lithium: C_{max} and AUC of lithium were non-significantly increased, but $T_{max}$of lithium was increased from 2, 4 hours to 3, 0 hours.	X	✓	✓	✓
Erythromycin: Non-significant increase in risperidone exposure	X	✓	✓	✓
7. Warnings				
Tardive dyskinesia: potentially irreversible, involuntary dyskinetic movements	✓	✓	✓	✓
Neuroleptic malignant syndrome: is a potentially fatal symptom	✓	✓	✓	✓
Concomitant use with furosemide: higher mortality in patients treated with furosemide and risperidone	✓	✓	✓	✓
Hyperglycaemia and diabetes mellitus: Hyperglycaemia, in some cases extreme and associated with ketoacidosis and hyperosmolar coma or death, has been reported in patients treated with risperidone	✓	✓	✓	✓

PRODUCT	RISPERDAL® (ORIGINATOR)	DRL-RISPERIDONE®	RISPACOR®	RISPERLET®
7. Warnings (Cont.)				
Cerebrovascular Adverse Events: accidents and transient ischemic attacks, have been reported during treatment with risperidone	✓	✓	✓	✓
Dementia associated with Parkinson's disease and senile dementia. Doctors should weigh the risks versus the benefits	✓	✓	✓	✓
Alpha-blocking activity. Due to the alpha-blocking activity of RIPERIDONE (orthostatic) hypotension can occur, especially during the initial dose-titration period.	✓	✓	✓	✓

Table 5: Reference Checklist 5 - Items for Assessing Agreement of Drug Information for venlafaxine. A Comparative Analysis between Effexor XR® & its Generics

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDOZ VENLA FAXINE XL®
1.Indications				
Depression, including depression with associated anxiety	✓	✓	✓	✓
Generalized anxiety disorder	✓	✓	✓	X
Social anxiety disorder	✓	✓	✓	X
Prevention of relapses of an episode of depression in patients responding to an initial 6-8 weeks of treatment	✓	✓	✓	✓
Prevention of recurrence in patients responding to 6 months of relapse prevention	✓	✓	✓	✓
2. Recommended Dosage				
Usual recommended dose is 75 mg once daily	✓	✓	✓	✓
If further clinical improvement is required, the dose may be increased to 150 mg once daily	✓	✓	✓	✓
If needed the dose can be further increased up to 225 mg, given once daily	✓	✓	✓	✓
The dose for depressed patients may be further increased if needed, up to 375 mg, given once daily	✓	✓	✓	X
The dose should then be gradually reduced consistent with patient response and tolerance	X	✓	✓	X
3. Precautions				
Use with caution in patients with recent history of myocardial infarction or unstable heart disease	✓	X	X	X
Effects in patients with recent history of myocardial infarction or unstable heart disease has not been evaluated to any appreciable extent	X	✓	✓	X
Dose related increases in blood pressure	✓	✓	✓	✓
Pre-existing hypertension should be controlled before treatment	✓	X	X	X
Caution in patients with underlying conditions that might be compromised by increases in blood pressure	✓	X	X	X
Increases in heart rate can occur, particularly with high doses	✓	X	X	X
Caution in patients with underlying conditions that might be compromised by increases in heart rate	✓	✓	X	✓
Convulsions may occur	✓	X	X	X
Introduced with care in patients with a history of convulsions	✓	X	X	X
Introduced with care in patients with a history of seizures	X	✓	✓	✓
Mania/Hypomania may occur in patients with mood disorders	✓	✓	X	✓
Use cautiously in patients with history or family history of bipolar disorder	✓	X	X	X
Aggression may occur in small portion of patients	✓	X	X	X

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDOZ VENLA FAXINE XL®
3. Precautions (Cont.)				
Dose reduction or discontinuation	✓	X	X	X
Use cautiously in patients with history of aggression	✓	X	X	X
Safety and efficacy in children under 18 years of age has not been established	✓	✓	✓	✓
Clinical trials in Major Depressive Disorder show increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm	✓	X	X	X
Cases of hyponatremia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur in volume depleted or dehydrated patients	✓	✓	✓	✓
Elderly patients, patients taking diuretics, and patients who are otherwise volume depleted, may be ay a greater risk	✓	X	X	X
Medicines that inhibit serotonin uptake may lead to abnormalities of platelet aggregation	✓	X	X	X
The risk of skin and mucous membrane bleeding, including gastrointestinal hemorrhage may be increased	✓	✓	✓	X
Use cautiously in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors	✓	X	X	X
Patients advised to notify their doctor if rash, hives or a related allergic phenomenon develops	✓	✓	✓	✓
Cautiously use in patients with moderate to severe renal impairment or cirrhosis of the liver	X	✓	✓	✓
Safety and efficacy in combination with weight loss agents including phentermine have not been established	✓	X	X	X
Co-administration with weight loss agents is not recommended	✓	X	X	X
Not indicated for weight loss alone or in combination with other products	✓	X	X	X
Associated with loss of appetite	X	✓	X	X
Dose-related weight loss	X	✓	✓	✓
Clinically relevant increases in serum cholesterol were recorded	✓	✓	✓	X
Association with Mydriasis risk for acute narrow angle glaucoma or with raised intra-ocular pressure should be monitored	X	✓	✓	X
Discontinuation effects are well-known to occur. Recommended to taper gradually and patient be monitored	✓	X	X	X
Symptoms associated with discontinuation, dose reduction or tapering: Hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue somnolence, paresthesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired co-ordination and balance, tremor, sweating, dry mouth, anorexia, diarrhea, nausea and vomiting.	✓	X	X	✓
Associated with impairment of judgment, thinking and motor skills	X	✓	✓	✓
Risk of suicide in depressed patients	✓	✓	✓	✓

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDOZ VENLA FAXINE XL®
4. Contraindications				
Hypersensitivity to any ingredient in the formulation	✓	✓	✓	✓
Use of Monoamine oxidase inhibitors (MAOI's) during therapy or 14 days after discontinuation of MAOI	✓	✓	✓	✓
Pediatric use: safety and efficacy has not been established	✓	✓	✓	✓
Safety during pregnancy and lactation has not been established	✓	✓	✓	✓
Hostility, suicidal ideation and self-harm reported in children	✓	X	X	X
5. Side effects				
Hostility, suicidal ideation and self-harm reported in children	X	✓	✓	✓
Asthenia	✓	✓	✓	✓
Headache	✓	✓	✓	✓
Pain	✓	X	X	X
Abdominal pain	✓	✓	✓	✓
Back pain	✓	✓	✓	✓
Chest pain	✓	✓	✓	✓
Photosensitivity reaction	✓	✓	✓	X
Hypertension	✓	✓	✓	✓
Vasodilation	✓	✓	✓	✓
Postural hypotension	✓	✓	✓	✓
Syncope	✓	✓	✓	X
Tachycardia	✓	X	✓	✓
Decreased appetite	✓	X	X	X
Constipation	✓	✓	✓	✓
Nausea	✓	✓	✓	✓
Vomiting	✓	✓	✓	✓
Ecchymosis	✓	✓	✓	✓
Increased serum cholesterol	✓	✓	✓	✓

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDOZ VENLA FAXINE XL®
5. Side effects (Cont.)				
Weight loss	✓	✓	✓	✓
Weight gain	✓	✓	✓	✓
Abnormal dreams	✓	✓	✓	✓
Decreased libido	✓	✓	✓	✓
Dizziness	✓	✓	✓	✓
Dry mouth	✓	✓	✓	✓
Hypertonia	✓	✓	✓	✓
Insomnia	✓	✓	✓	✓
Nervousness	✓	✓	✓	✓
Paresthesia	✓	X	✓	✓
Sedation	✓	✓	✓	X
Tremor	✓	✓	✓	✓
Apathy	✓	✓	✓	X
Hallucinations	✓	✓	✓	X
Myoclonus	✓	✓	✓	X
Convulsion	✓	✓	✓	X
Manic reaction	✓	✓	✓	✓
Yawning	✓	✓	✓	✓
Rash	✓	✓	✓	✓
Abnormality of accommodation	✓	✓	✓	✓
Mydriasis	✓	✓	✓	✓
Depersonalization	✓	✓	✓	✓
Paresthesia	✓	✓	✓	✓
Vertigo	X	✓	✓	✓
Dystonia	✓	✓	✓	X
Arthralgia	X	✓	✓	✓
Visual disturbance	✓	X	X	X
Altered taste sensation	✓	✓	✓	✓

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDO Z VENLA FAXINE XL®
5. Side effects (Cont.)				
Abnormal ejaculation/orgasm (males)	✓	✓	✓	✓
Anorgasmia	✓	✓	X	✓
Erectile dysfunction	✓	✓	✓	X
Impaired urination (mostly hesistancy)	✓	✓	✓	X
Abnormal orgasm (females)	✓	X	✓	✓
Urinary retention	✓	✓	✓	✓
Agranulocytosis	✓	✓	✓	✓
Aplastic anemia	✓	✓	✓	✓
Neutropenia	✓	✓	✓	✓
Pantocytopenia	✓	X	✓	✓
Hyperaesthesia	X	✓	✓	✓
Abnormal vision	X	✓	✓	✓
Migraine	X	✓	✓	✓
Dyspnea	X	✓	✓	✓
Bronchitis	X	✓	✓	✓
Anorexia	✓	✓	✓	✓
Nausea	✓	✓	✓	✓
Vomiting	✓	✓	✓	✓
Neck pain	X	✓	✓	✓
Reported during post-marketing surveillance *Body as a whole:* Chills	✓	✓	✓	✓
Angioedema	✓	✓	✓	✓
Anaphylaxis	✓	✓	✓	X
Cadiovascular Palpitations	✓	✓	✓	✓
Hypotension	✓	✓	✓	✓
OT prolongation	✓	✓	✓	X
Ventricular fibrillation	✓	✓	✓	X
Ventricular tachycardia (including Torsades de Pointes)	✓	✓	✓	X
Digestive system Bruxism	✓	✓	✓	X
Diarrhea	✓	✓	✓	✓
Gastrointestinal hemorrhage	✓	X	X	✓
Pancreatitis	✓	✓	✓	X
Anorexia	✓	✓	✓	✓
Increased appetite	✓	✓	✓	✓
Dyspepsia	✓	✓	✓	✓
Eructation	✓	✓	✓	✓
Flatulence	✓	✓	✓	✓

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDOZ VENLA FAXINE XL®
5. Side effects (Cont.)				
Haematologic and lymphatic system Mucous membrane bleeding	✓	✓	✓	✓
Prolonged bleeding time	✓	✓	✓	✓
Gynecological bleeding	✓	X	X	✓
Thrombocytopenia	✓	✓	✓	✓
Blood dyscrasias	✓	X	X	✓
Metabolic Abnormal liver function tests	✓	✓	✓	X
Hyponatremia	✓	✓	✓	✓
Hepatitis	✓	✓	✓	X
Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)	✓	✓	✓	✓
Increased prolactin	✓	✓	✓	X
Musculoskeletal Rhabdomyolysis	✓	✓	✓	X
Myalgia	✓	✓	✓	✓
Central nervous system Headache	✓	✓	✓	✓
Confusion	✓	✓	✓	✓
Depersonalization	✓	✓	✓	✓
Agitation	✓	✓	✓	✓
Impaired co-ordination and balance	✓	X	X	X
Akathisia/psychomotor restlessness	✓	X	X	X
Neuroleptic malignant syndrome (NMS)	✓	✓	✓	X
Serotonergic syndrome	✓	✓	✓	X
Delirium	✓	✓	✓	X
Extrapyramidal reactions	✓	✓	✓	X
Tardive dyskinesia	✓	✓	✓	X
Aggression	✓	X	X	X
Amnesia	✓	✓	✓	✓
Anxiety	✓	✓	✓	✓
Depression	✓	✓	✓	✓
Emotional labiality	✓	✓	✓	✓
Hypoesthesia	✓	X	X	X

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDOZ VENLA FAXINE XL®
5. Side effects (Cont.)				
Somnolence	✓	✓	✓	✓
Abnormal thinking and trismus	✓	✓	✓	✓
Twitching	X	✓	✓	✓
Respiratory Pulmonary eosinophilia	✓	✓	✓	X
Pharyngitis	✓	✓	✓	✓
Rhinitis	✓	✓	✓	✓
Skin Sweating	✓	✓	✓	✓
Alopecia	✓	✓	✓	X
Erythema multiforme	✓	✓	✓	X
Stevens-Johnson Syndrome	✓	✓	✓	X
Pruritus	✓	✓	✓	✓
Urticaria	✓	X	X	X
Toxic epidermal necrolysis	✓	X	X	X
Special senses Tinnitus	✓	✓	✓	✓
Angle closure glaucoma	✓	X	X	X
Urogenital Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g. menorrhagia, metrorrhagia)	✓	✓	✓	X
Increased urinary frequency	✓	✓	✓	✓
Urinary incontinence	✓	X	X	X
Impotence	X	✓	✓	✓
6. Interactions				
Must not be initiated for at least 14 days after discontinuation of treatment with MAOI (Monoamine Oxidase Inhibitors)	✓	✓	✓	✓
CNS active medicines Caution is advised when taken in combination with other CNS-active medicines	✓	✓	✓	X
Based on known mechanism of action and potential for serotonin syndrome, caution is advised when co-administered with other medicines that may affect the serotonergic neurotransmitter system (such as triptans, SSRI's, lithium, sibutramine, tramadol or St. John's Wort. Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms	✓	✓	✓	✓
If concomitant treatment of venlafaxine with an SSRI, an SNRI or a 5-hydroxytrytamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.	✓	X	X	X

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDOZ VENLA FAXINE XL®
6. Interactions (Cont.)				
The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended	✓	X	X	X
Indinavir A pharmacokinetic study with Idinavir has shown a 28 % decrease in AUC and a 36 % decrease in $C_{max}$for Indinavir. Idinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown	✓	✓	✓	✓
Warfarin Venlafaxine may result in increased anticoagulant effects if co-administered	X	✓	✓	✓
Ethanol Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However patients should be advised to avoid alcohol consumption	✓	X	X	X
Haloperidol A pharmacokinetic study with haloperidol has shown for haloperidol a 42% decrease in total oral clearance, a 70 % increase in AUC, an 88% increase in C_{max}, but no change in half-life. This should be taken into account in patients treated with haloperidol concomitantly	✓	✓	✓	✓
Cimetidine At steady state cimetidine has been shown to inhibit first-pass metabolism of venlafaxine	✓	✓	✓	✓
Imipramine Imipramine dos not affect the venlafaxine and O-desmethylvenlafaxine	✓	✓	✓	✓
Ketoconazole Extensive and poor metabolizers of CYP2D6 results in higher plasma concentrations of both venlafaxine and O-desmethylvenlafaxine	✓	X	X	X
Metoprolol Increased plasma concentration metoprolol by approximately 30-40%. Caution should be exercised with co-administration	✓	X	X	X
Risperidone Increase in Risperidone AUC by 32% Clinical significance unknown	✓	✓	✓	✓
Diazepam Does not appear the pharmacokinetics of either venlafaxine or O-desmethylvenlafaxine	✓	✓	✓	✓
Lithium Venlafaxine has no effects on the pharmacokinetics of lithium	✓	✓	✓	✓
Medicines highly bound to plasma proteins Venlafaxine is not highly bound to plasma proteins (27% bound), administration of venlafaxine with another medicine that is highly protein bound is not expected to cause increased free concentrations of the other medicine	✓	✓	✓	✓
Medicines metabolized by cytochrome P450 isoenzyme Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4, CYP1A2 and CYP2C9.	✓	✓	✓	✓

PRODUCT	EFFEXOR XR® (ORIGINATOR)	VENLOR XR®	VENLA FAXINE XR®	SANDOZ VENLA FAXINE XL®
7. Warnings				
All patients should be monitored for clinical worsening and suicidality	✓	X	✓	X
Alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression , and suicidal ideation especially when initiating therapy or during any change in dose or dosage regimen	✓	✓	✓	X
Risk of suicide attempt must be considered especially in depressed patients	✓	✓	X	X
Smallest quantity of medicine, consistent with good patient management, should be provided to reduce the risk of overdose	✓	✓	X	X
Serotonin syndrome	✓	X	X	X
Mydriasis	✓	X	X	X
Patients with raised intra-ocular pressure or at risk for acute narrow angle glaucoma recommended to be closely monitored	✓	X	X	X
Safety and efficacy in children under 18 years of age have not been established	✓	X	✓	✓
Patients with major depressive disorder may experience worsening of their depression and/or emergence of suicidal ideation whether or not they are taking antidepressants	✓	✓	✓	X
Same precautions should be observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.	✓	✓	✓	✓
The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility	✓	✓	✓	✓
Although a causal link between emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing Venlafaxine in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms	✓	✓	✓	✓
If the decision is made to discontinue treatment, Venlafaxine should be tapered	✓	✓	✓	✓

3.2 Degree of Information Agreement between the originator product and generics

Tables 6a to 10c summarise the data presented in the comparative analysis between the originator products and their generics, shown above. This concise summary is presented below in a scorecard. The % Agreement was calculated by dividing the number of similarities present in the generic PI by the total items present in the innovator PI and this was repeated for each category.

Table 6a: Scorecard for fluoxetine (Lilly – Fluoxetine®) - Clone

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	6	11	4	77	9	3
Additions	0	0	0	0	0	0	0
Omissions	0	0	0	0	0	0	0
Agreement with Innovator PI (%)	3/3 (100%)	6/6(100 %)	11/11 (100%)	4/4 (100%)	77/77 (100%)	9/9 (100%)	3/3 (100%)

Table 6b - Scorecard for fluoxetine (Nuzak®) registered by CiplaMedpro

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	3	7	3	47	9	1
Additions	0	0	6	4	3	0	1
Omissions	0	3	4	1	30	0	2
Agreement with Innovator PI (%)	3/3 (100%)	3/6(50%)	7/11 (64%)	3/4 (75%)	47/77(6 1%)	9/9 (100%)	1/3 (33%)

Table 6c - Scorecard for fluoxetine (Lorien®) registered by Aspen Pharmacare

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	3	8	3	48	9	1
Additions	0	0	0	2	3	0	0
Omissions	0	3	3	2	29	0	2
Agreement with Innovator PI (%)	3/3 (100%)	3/6(50%)	8/11 (73%)	3/4 (75%)	48/77 (62%)	9/9 (100%)	1/3 (33%)

Table 7a - Scorecard for citalopram (Cilift®) registered by Aspen Pharmacare

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	2	5	No info under this heading for originator	3	34	2	4
Additions	0	0	N/A	0	1	1	0
Omissions	1	1	N/A	0	2	0	0
Agreement with Innovator PI (%)	2/3 (67%)	5/6 (83%)	N/A	3/3 (100%)	34/36 (94%)	2/2 (100%)	4/4 (100%)

Table 7b - Scorecard for citalopram (DRL-Citalopram®) registered by Dr Reddy's Laboratories

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	6	No info under this heading for originator	3	36	2	4
Additions	0	0	N/A	2	0	4	9
Omissions	0	0	N/A	0	0	0	0
Agreement with Innovator PI (%)	3/3 (100%)	6/6 (100%)	N/A	3/3 (100%)	36/36 (100%)	2/2 (100%)	4/4 (100%)

Table 7c - Scorecard for citalopram (Citalohexal®) registered by Hexal

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	6	No info under this heading for originator	3	36	2	2
Additions	0	0	N/A	2	1	1	1
Omissions	0	0	N/A	0	0	0	2
Agreement with Innovator PI (%)	3/3 (100%)	6/6 (100%)	N/A	3/3 (100%)	36/36(100%)	2/2 (100%)	2/4 (50%)

Table 8a - Scorecard for sertraline (Serlife®) registered by Ranbaxy

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	2	2	2	2	43	18	15
Additions	0	0	4	1	0	0	0
Omissions	2	2	16	3	8	1	1
Agreement with Innovator PI (%)	2/4 (50%)	2/4 (50%)	2/18 (11%)	2/5 (40%)	43/51 (84%)	18/19 (95%)	15/16 (94%)

Table 8b - Scorecard for sertraline (Aspen Sertraline®) registered by Aspen Pharmacare

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	3	3	2	51	19	14
Additions	0	0	4	1	0	1	0
Omissions	1	1	15	3	0	0	2
Agreement with Innovator PI (%)	3/4 (75%)	3/4 (75%)	3/18 (17%)	2/5 (40%)	51/51 (100%)	19/19 (100%)	14/16 (88%)

Table 8c - Scorecard for sertraline (Serdep®) registered by CiplaMedpro

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	3	2	4	51	19	14
Additions	0	0	4	0	0	1	0
Omissions	1	1	16	1	0	0	2
Agreement with Innovator PI (%)	3/4 (75%)	3/4 (75%)	2/18 (11%)	2/5 (80%)	51/51 (100%)	19/19 (100%)	14/16 (88%)

Table 9a - Scorecard for risperidone (DRL-Risperidone®) registered by Dr Reddy's Laboratories

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	10	6	3	39	8	7
Additions	0	0	4	1	0	4	0
Omissions	0	0	0	0	0	0	0
Agreement with Innovator PI (%)	3/3 (100%)	10/10 (100%)	6/6 (100%)	3/3 (100%)	39/39 (100%)	8/8 (100%)	7/7 (100%)

Table 9b - Scorecard for risperidone (Rispercor®) registered by Accord

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	10	6	2	39	7	7
Additions	0	0	5	1	0	4	0
Omissions	0	0	0	0	0	1	0
Agreement with Innovator PI (%)	3/3 (100%)	10/10 (100%)	6/6 (100%)	2/3 (67%)	39/39 (100%)	7/8 (88%)	7/7(100%)

Table 9c - Scorecard for risperidone (Risperlet®) registered by Janssen-Cilag (Clone)

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	10	6	2	39	7	7
Additions	0	0	5	1	0	4	0
Omissions	0	0	0	0	0	1	0
Agreement with Innovator PI (%)	3/3 (100%)	10/10(100%)	6/6 (100%)	2/3 (67%)	39/39 (100%)	7/8 (88%)	7/7 (100%)

Table 10a - Scorecard for venlafaxine (Venlor XR®) registered by CiplaMedpro

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	5	4	9	4	103	12	8
Additions	0	1	7	0	10	1	0
Omissions	0	0	19	1	16	5	5
Agreement with Innovator PI (%)	5/5 (100%)	4/4 (100%)	9/28 (32%)	4/5 (80%)	103/120 (86%)	12/17 (71%)	8/13 (62%)

Table 10b - Scorecard for venlafaxine (Venlafaxine XR®) registered by Adcock Ingram

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	5	4	7	4	105	13	8
Additions	0	1	6	0	10	0	0
Omissions	0	0	21	1	14	5	5
Agreement with Innovator PI (%)	5/5 (100%)	4/4 (100%)	7/28 (25%)	4/5 (80%)	105/120 (88%)	13/17 (76%)	8/13(62%)

Table 10c - Scorecard for venlafaxine (Sandoz Venlafaxine®) registered by Sandoz

	Indications	Dosage	Precautions	Contra-indications	Side effects	Interactions	Warnings
Similarities	3	3	8	4	80	12	5
Additions	0	0	4	0	10	0	0
Omissions	2	1	20	1	41	6	8
Agreement with Innovator PI (%)	3/5 (60%)	3/4 (75%)	8/28 (29%)	4/5 (80%)	80/120 (67%)	12/17 (71%)	5/13 (38%)

Table 11: Summary of Scorecards for all products used in this study

Trade Name of Generic Product	Indications (% Agreement)	Dosage (% Agreement)	Precautions (% Agreement)	Contra-Indications (% Agreement)	Side Effects (% Agreement)	Interactions (% Agreement)	Warnings (% Agreement)	Total Agreement with innovator PI for all headings (Yes or No)
Fluoxetine								
Lilly – Fluoxetine®*	100	100	100	100	100	100	100	Yes
Nuzak®	100	50	64	75	61	100	33	No
Lorien®	100	50	73	75	62	100	33	No
Citalopram								
Cilift®	67	83	N/A	100	94	100	100	No
DRL-Citalopram®	100	100	N/A	100	100	100	100	Yes
Citalohexal®	100	100	N/A	100	100	100	50	No
Sertraline								
Serlife®	50	50	11	40	84	95	94	No
Aspen Sertraline®	75	75	17	40	100	100	88	No
Serdep®	75	75	11	80	100	100	88	No
Risperidone								
DRL-Risperidone®	100	100	100	100	100	100	100	Yes
Rispercor®	100	100	100	67	100	88	100	No
Risperlet®*	100	100	100	67	100	88	100	No
Venlafaxine Hydrochloride								
Venlor XR®	100	100	32	80	86	71	62	No
Venlafaxine XR®	100	100	25	80	88	76	62	No
Sandoz Venlafaxine®	60	75	29	80	67	71	38	No

*clone

3.3 Discussion of Results

Accumulated data on five molecules in the CNS field revealed that some results were as expected and some results were of concern. Lilly-Fluoxetine, a clone was identical to the innovator Prozac® but the same cannot be said for Risperlet® which is also a clone. The scorecard for Risperlet® (Table 9c) shows that it is partially in agreement with the innovator under the categories; "*Contra-indications*" and "*Interactions*". A few other notable discoveries will be discussed later on.

The MCC's policy is that generic package inserts should be standardized on the originator package insert for a given medicine.[5] With this in mind, the degree of information agreement between the innovator product and its three generics, which have been registered by MCC in South Africa, are surprisingly low. There are only 2 occasions when all 3 generic brands have the same information as the innovator under the categories analysed ("*Indications*", "*Dosage*" , "*Precautions*", "*Contra-indications*", "*Side effects*", "*Interactions*" and "*Warnings*").These products are Lilly-Fluoxetine® (clone) and DRL- Risperidone®. Lilly-Fluoxetine® is a clone of Prozac® thus making it an exact copy of the innovator. The applicant is the holder of the certificate of registration for both products which would explain why these package inserts are identical and thus no copyright infringement occurred.

In the Citalopram class, Table 7b reveals that DRL-Citalopram® is the only product that exhibits 100 % agreement with the innovator under all headings except "*Precautions*". This is because the innovator package insert combines "*Precautions*" with "*Side Effects*". While this may look like an elegant solution for streamlining information, collapsing two categories into one means that the potential severity of the precautions can be lost as they are not emphasised enough. For example, one important precaution involves closely monitoring patients during early therapy as suicide is an inherent risk in depressed patients. This is not highlighted when the two categories are combined and this risk loses its importance when placed in-between some of the common side effects. Embedding this risk with others means that it is likely that this precaution could be missed by a reader. Risperidone (Tables 9a-c) is the only molecule where all three generic products are in complete agreement with the innovator regarding information listed under "*Indications*", "*Dosage*",

"*Precautions*", "*Side effects*" and "*Warnings*". In contrast, it was noted that the dosage recommendation diverged for the other molecules e.g. only two out of three generic brands were in complete agreement with the originator package insert for citalopram and venlafaxine, whilst no generic brands were in complete agreement with the originator package insert for sertraline pertaining to dosage.

These differences are of concern because the clinical and efficacy studies for the drug substance, would presumably relate to the original studies performed during the developmental stage of the medicine, and should therefore be consistent across all generic brands. This raises the question if these studies were accepted for the innovator, why were they excluded from the generics?

However these findings are similar to those of a WHO international study regarding the national comparisons of materials for different brands of the same drug substance[22.] The majority of various brands of ciprofloxacin and fluoxetine were in extremely low agreement with the reference regarding "*side-effects*" and "*precautions*", and incomplete agreement for "*indications*" and "*recommended dosage*"; incomplete agreement was also found for various brands of nifedipine across "*Indications*", "*Recommended dosage*", "*Side-effects*" and "*Precautions*". The WHO reporting on similar studies comparing ciprofloxacin and fluoxetine have revealed poor convergence of PI information with the innovator.

The U.S Food and Drug Administration as well as other international countries pay close attention to the labelling of medicines. Due to pharmaceutical products being distributed via various legal channels, labelling of medicines and the package insert becomes very important. The majority of medicines exported from the United States are in bulk form and are repackaged and labelled in the country of marketing authorisation.[23]A widely quoted study by the United States Office of Technology Assessment found that up to two thirds of pharmaceuticals sold by US companies in developing countries were mislabelled.[24] The report found that "*Warnings*" and "*Precautions*" were underestimated and clinical as well as descriptive pharmacological information was lacking in many foreign labels. Unfortunately one of the reasons this may arise is due to the various regulatory authorities having different labelling requirements for the same pharmaceutical product. If generics are

bioequivalent to their innovator and may be safely interchanged for the innovator, then there should be no differences regarding labelling and more specifically information present in the package inserts. A closer look at the three generics; Serlife®, Aspen Sertraline® and Serdep® in Table 11 reflect that there is a 83% non-compliance under the category of "*Precautions*" for Aspen Sertraline®. Moreover there is 89 % non-compliance under the same category for Serlife® and Serdep®. This data does little to encourage the use of generics.

Two molecules namely venlafaxine and fluoxetine were chosen to be discussed in greater detail by means of a textual analysis of the "*Side effects*" present. Fluoxetine was chosen because it highlights the whole constellation of missing information that is only directed to the female consumer. Venlafaxine was the other molecule chosen because it showed the highest impact on patient safety where the most troubling issues were found in the innovator package insert. When one closely analyses the texts for what is present and absent across the products, a range of interesting and startling findings come to light.

3.3.1 Textual Analysis of fluoxetine

The textual analysis of fluoxetine revealed a lack of clarity in relation to dosage. An example of this is the way in which Nuzak® fails to include the following information:

- Doses above 80 mg/day are not recommended for any indication (Table 1)

Nuzak® also states that the recommended maximum dose for elderly patients to be three times the recommended dose instructed in the innovator (Nuzak® 60 mg vs Prozac® 20 mg). Moreover, Lorien® not only fails to include the recommended dosage for elderly patients but includes information pertaining to the maximum recommended dosage of 80 mg/day under the specific condition, Major Depressive episodes. There is a high probability that this would be incorrectly interpreted, in that 80 mg/day is only applicable to major depression and not applicable to the other indications such as Bulimia Nervosa and Obsessive Compulsive Disorder. The researcher considers this finding in relation to the authors' stance to vulnerable minority groups.

This case could be built when one considers the issue of female health. There is a startling discrepancy in Nuzak® and Lorien's lack of reference to side effects that would be experienced solely by females (refer to Table 1 under "*Side Effects*"). Prozac® clearly lists twelve side effects directed to the female patient. Data from the National Health and Nutrition Examination Surveys, 2005-2008 found that overall, females are 2½ times as likely to take antidepressant medication as males.[25] Bearing in mind that more females take antidepressants, a lack of information may be regarded as a violation of female consumers' right to information about their own health. One possible reason why Nuzak® and Lorien® don't report side effects experienced only by women is so not to frighten away the female patient especially since women make up the bulk of the market. However, limited access to the correct information impedes women's decision making processes which results in uninformed choices about women's own health and their bodies. This is possibly a good example of how a capitalist discourse shapes medical discourses.

When the side effects of fluoxetine generic products were compared to the innovator, Prozac®, the following differences were noted.

- Hallucinations (Prozac®) versus Abnormal dreams (Nuzak® and Lorien®)
- Increased libido (Prozac®) versus Decreased libido (Nuzak® and Lorien®)
- Weight gain (Prozac®) versus Loss of mass (Lorien®)
- Increased salivation (Prozac®) versus Dry mouth (Nuzak® and Lorien®)

These results are congruent with the inconsistencies seen with venlafaxine as noted with "increased libido" versus "decreased libido". This pattern may be further validated by the direct contradiction of "Increased salivation" in Prozac® to "dry mouth" in the generic package insert.

The issue of women's access to information can be raised again when one analyses the terms "weight gain" and "loss of mass". Firstly "loss of mass" is a term that is ambiguous because it could also mean the loss of water mass or even the loss of

muscle mass. For the sake of this argument it is assumed that "loss of mass" is “weight loss" which is how it is likely to be interpreted by a lay person. "Weight loss" does not mean "weight gain" on any level in any language. Fairclough would argue that the inclusion or exclusion of words or phrases in a particular discourse is not random. We live in a society where the topic of weight is an obsession and an even bigger issue for women, so this would raise the question whether the author of the package insert for Lorien® omitted "weight gain" intentionally and used the words "loss of mass" as a marketing tool. The semantic cluster which re-enforces the choice of using "loss of mass" over "weight gain" rules this out as an oversight and it appears that the idea of weight loss remains. One could argue that the semantic choices of “weight gain” further make the case about gender discrimination against women. Added to this is the relationship between gender and capitalism where profit is a driver that shapes the construction of a text that purports to be objective.

The words "appetite loss" and "anorexia" presented under side effects for Lorien® are words that are associated with weight loss and conducive of losing weight. This finding would require further analysis across a broader range of samples.

The innovator package insert is in itself contradictory in stating that a common side effect experienced when taking fluoxetine is a gain in weight but under “*Precautions*” states that “Prozac® may cause loss of mass which could be undesirable in under mass depressed patients." This is a cause for concern as the innovator package insert is the basis for information on which generic package inserts are derived. This raises many concerns about the accuracy of information present in package inserts, the ways in which a level of ambiguity is introduced that works to the advantage of pharmaceutical companies sales’, the rights of female and elderly patients and raises questions about the evaluation process in registering medicines in South Africa.

3.3.2 Textual Analysis of venlafaxine

A closer look at the innovator package insert and the generics for venlafaxine, indicate that the results do not in fact exhibit total concordance with the innovator product. The first finding is related to the innovator itself. A discrepancy exists where a statement is omitted from the originator's own package insert, namely the statement regarding dosage adjustment where, once the maximum daily dose of 375 mg is given, the dose should be gradually reduced to be consistent with patient response and tolerance. Good patient management involves therapeutic drug monitoring which is a useful tool in providing information necessary for dose adjustment. It provides a means of assessing compliance, ensuring an effective concentration, and avoiding toxicity. Unfortunately, this was not evident with Effexor XR®.

The omissions in the innovator PI extend further into "*Interactions*". It is interesting to note that there is no mention of the interaction between venlafaxine and warfarin in the innovator package insert of venlafaxine but the resultant increased anticoagulant effect is present in the three generic product brands. This may be an oversight but it is a major concern for safety reasons, particularly in special populations such as geriatric patients who are more susceptible to anticoagulant effects. This anomaly is seen again with citalopram, where only the generic brand DRL-Citalopram® (Table 2) makes mention of the interaction with warfarin whilst the other two generic brands and innovator product fail to do so. One of the reasons for the pattern seen above could be that the safety information on many package inserts has not undergone any updating in line with post-marketing surveillance studies or international database references.

When the "*Side effects*" of venlafaxine generic products were compared to the innovator Effexor®, the following differences were noted.

- Decreased appetite (Effexor®) versus Increased appetite (Sandoz Venlafaxine®)

- Sedation (Effexor®) versus Somnolence (Sandoz Venlafaxine®) under Nervous system disorders

- Hallucinations (Effexor®) versus Abnormal dreams (Sandoz Venlafaxine®)

- Dystonia (Effexor®) versus Hypertonia (Sandoz Venlafaxine®)

- Visual disturbance (Effexor®) versus Abnormal vision (Sandoz Venlafaxine®)

- Hypoaesthesia (Effexor®) versus Hyperaesthesia (Venlor XR®)

- Gastrointestinal haemorrhage (Effexor®) versus Gastrointestinal complaints (Venlafaxine XR Adco®)

These examples indicate completely opposite meanings of a range of side effects reported in the innovator and generic package. These differences are reflected in the adjectives used to describe nouns, for example ‘decreased’ appetite and; ‘increased’ appetite. Most people understand the difference between the two. The use of prefixes also shifts the meanings of words. In the case of aesthesia, the prefix hypo- denotes deficiency, lack or small size whilst the opposite prefix, hyper- denotes excessive, or abnormally increased. Another marked example of contradictory meanings is demonstrated by altering nouns: the generic manufacturer replaces "gastrointestinal haemorrhage" with "gastrointestinal complaints". Replacing ‘haemorrhage’ with ‘complaints’ downplays the severity of the side effect. "Haemorrhage" or bleeding is defined by the Oxford Medical Dictionary as the escape of blood from a ruptured blood vessel, externally or internally. Damage to minor vessels may produce only an oozing. Rupture of a major blood vessel can lead to the loss of several litres of blood in a few minutes, resulting in shock, collapse and death if untreated[26], whilst gastrointestinal complaints are a common medical occurrence. Most people have experienced an upset stomach, indigestion, nausea,

vomiting, gas in the gastrointestinal tract, or changes in bowel habits (e.g. diarrhoea, constipation). These are not fatal.

3.3.3 Ordering Principles of Side Effects

The FDA considers the ordering of risks within a package insert or patient information leaflet an important factor in determining the risk profile conveyed by text regardless of whether it is directed toward healthcare professionals or consumers. In order to demonstrate this, we have chosen Nuzak® capsules as an example to analyse the ordering principles of side effects. (Refer to Appendix 1, for a detailed look at the information presented by the applicant, CiplaMedpro.)

Firstly, the frequency of events has not been stated, leaving the prescriber to decipher how common, uncommon or rarely the events may occur. Secondly, it is difficult to assess which side effects are of greater importance especially since the list is quite extensive. From the perspective of a healthcare professional, this information would be used to not only base part of their decision in prescribing the medicine, but also equip the healthcare professional with information to better inform the patient of possible side effects as well as the frequency of effects that could be experienced and thus possibly ensure patient compliance.

Memory research consistently shows that, in an experimental setting, when people process an entire list or text, they are better able to recall items at the beginning and the end than items in the middle.[10] When reading printed material, readers may lose interest toward the end of a lengthy paragraph and it is not likely that the information at the end will be as well comprehended as the information at the beginning. If a medicine's most important risks are located in the middle of such a list these important risks may not be effectively retained.

Compliance with treatment or treatment adherence is a very important clinical issue. Many mental disorders require more than a brief medication intervention, for some patients, treatment with a prescribed antidepressant can last anything from several months to years or even lifelong therapy.[27] According to a study published in the Psychiatric Times, one factor affecting patients' compliance with medication is

medication characteristics. These characteristics include side effects, individual sensitivity to side effects and simple versus complicated medication regimens. Taking into account the ordering principles of side effects presented in the package insert for all five molecules studied, it is very difficult to ascertain the most important information is from the less important information. This has a major impact not only on the prescriber who has to make the final decision in prescribing such medication but also on the patient who has to take the medication.

Chapter 4: Conclusions and Recommendations

The results obtained from this study demonstrate that package inserts of approved products currently circulating in South Africa show considerable differences between the originator product and subsequent generic brands of the same drug substance. Not only does this study further validate previous research conducted in this area but it is also a novel study in that it uses a textual analysis to identify patterns emerging from the checklist data.

To summarise, the above results are concerning in terms of the provision of information that is consistent, complete, accurate, internationally-harmonised and contain updated dosing and safety data, because non-compliance would result in potentially harming the patient. This research has also highlighted important issues facing labelling in the South African registration process. It raises the questions about where information is sourced for generic medicines, the issue of accuracy when generic package inserts are written as well as the integrity of the pharmaceutical companies who are marketing and selling their products with package inserts that are either deficient in providing information or providing information that is incorrect and thus misinform the prescriber and end user. Despite the fact that this study is based on a small sample size, there appears to be significant findings. Data demonstrates inconsistencies across the products analysed. This makes one question whether this pattern is prevalent with other widely used generics. Acute and other chronic medication would be an ideal starting point for further study. Moreover a startling discovery that should be noted is that side effects experienced solely by women were omitted from two out of three generics. This is a topic that should be addressed with urgency considering the high level of usage of antidepressants where the figures show that women are 2 ½ times more likely to use these medicines than men.[16]

The following recommendations are made, based on the findings in this study.

- A mandatory updating system should be introduced by MCC where the timeframes are legislated for both the frequency of updating and the time period for the implementation of updated materials following approval by MCC as well as a penalty system for offenders.

- MCC could send out notification letters to the applicant with updated information and required changes to be implemented in their package inserts within a specified timeframe.
- Like the Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA), the regulatory authority in South Africa can implement a boxed warning, more commonly referred to as a “black box” warning. These could feature prominently in the labelling of medicines to warn prescribers and patients about serious adverse reactions or special precautions.
- Investigate the process that is undertaken by Registration pharmacists in populating package inserts.
- New information from post-marketing surveillance studies should be referenced.
- Further studies should be conducted on other classes of medicines so we can compare the trends regarding omissions, additions and slippage.
- Side effects solely experienced by females were omitted from package inserts which is very concerning. This warrants further investigational studies. These results can then be used to actively address this problem and enforce mechanisms to ensure compliance with the innovator.
- The findings also highlight specific areas of concern such as ordering principles of side effects. Although individual side effects are important to a patients’ health, the ordering (word placement) of these side effects are just as important. The ordering in which the side effects are presented has an influence on the risk profile conveyed by this section within the PI. This would need to be investigated further as this report shows some areas of concern.

Due to the limited of scope of this study, the other categories in the PI’s are not reflected but a more detailed analysis of PI’s need to be made across all categories within the insert. These findings could be used as a foundation for further study of package inserts using a larger sample size across various drug classes to better understand gaps in the information provided. This would allow us to begin the

process of addressing and validating shortfalls with the current regulatory policies and processes in South Africa which govern labelling of pharmaceutical product.

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