A comparison of the information used to populate patient information leaflets for complementary medicines with recommended references, and an analysis of the type and order of language used.

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

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Declaration

I, Catherine Forbes, declare that this research 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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Catherine Forbes

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Abstract

Regulations published by the Medicines Control Council (MCC), the regulatory body that existed before the South African Health Products Regulatory Authority (SAHPRA), required Complementary and Alternative medicines to demonstrate the safety, quality and efficacy of the product. Package Inserts (PIs) and Patient Information Leaflets (PILs) needed to comply with the MCC's Guidelines. Four package inserts from four different complementary products were compared and analysed. Biral® and Calmettes Nite tablets, containing Valerian Root, and Flora Force St John's wort and Wellvita St John's wort were examined. The package inserts were evaluated for compliance to the published Guidelines for Package Inserts, and the information presented was validated according to published references in a literature review. The package inserts were compared according to active ingredient. The information available to the patient was evaluated using the principles of Critical Discourse Analysis. The findings showed there were discrepancies in compliance to the Guidelines; the Valerian Root PIs were more compliant than the St John's wort PIs. Biral® and Calmettes Nite tablets contained similar information with Calmettes presenting more clinical information. Both inserts had sections that were appropriate for the non-medical reader, and areas that are confusing. The Flora Force St John's wort PI used few full sentences and relied on medical terminology throughout the insert. It was significantly shorter than the Wellvita St John's wort PI. The Wellvita St John's wort PI was simply written, until the sections on Side Effects and Interactions, where medical terminology and abbreviations were used. All four products presented themselves as natural remedies. While the information contained in the PI can be validated in published literature, more oversight of these inserts is required from the SAHPRA.

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List of Abbreviations Used

5HTP	5 hydroxytryptophan
ADHD	Attention Deficit Hyperactivity Disorder
AUC	Area under the curve
CAMs	Complementary and Alternative Medicines
Cmax	Peak serum concentration
CDA	Critical Discourse Analysis
CNS	Central Nervous System
DSM-5	Diagnostic and Statistical Manual 5^{th} edition
EU	European Union
GABA	gamma-aminobutyric acid
$GABA_A$	gamma-aminobutyric acid Subunit A
GAD	Generalised Anxiety Disorder
MAO-inhibitors	Monoamine Oxidase Inhibitors
MCC	Medicines Control Council
NAPPI	National Pharmaceutical Product Index
OTC	Over the counter
PAR	Public Assessment Report
PI	Package Insert
PIL	Patient Information Leaflet
SAHPRA	South African Health Products Regulatory Authority
SSRI	Selective Serotonin Reuptake Inhibitors

UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

Chapter 1: Introduction

Complementary and Alternative Medicine (CAMs) products are increasingly being used to treat ever expanding conditions (Owens, Bergens & Puckett, 2014). They are available in all retail pharmacies, ready to buy off the shelf with no input or counselling from a healthcare professional, and many more of them are available to purchase online. On the other hand, the purchase of over-the-counter (OTC) products can only happen through an interaction with a health care professional, such as a pharmacist, a pharmacist's assistant, or doctor. A common belief among the non-medical community is that natural medicines are safe, with no side effects. In truth, many of our most potent medicines today are derived from plants, for example digitalis, extracted from the foxglove flower, which is fatal in small doses.

In July 2011, the Minister of Health published an amendment to the Regulations to the Medicines and Related Substances Control Act 101 of 1965, calling for the regulatory control of Complementary and Alternative Medicines. The then Medicines Control Council (MCC) conducted an audit of CAMs products to determine what products were available, and what claims were made. Manufacturers of CAMs products were called upon to submit an application that showed the safety, efficacy and quality of their product as part of the audit process. The MCC provided manufacturers of CAMs with an abridged application form which requested only administrative information, a copy of the label and package insert, the unit formulation, and a list of countries where the product was sold (Fourie *et al,* 2017). The abridged application form requested very little information and did not facilitate the original mandate to audit the quality, safety and efficacy of these products (Fourie *et al,* 2017). Over 25 000 complementary and traditional medicines have been submitted to the South African Health Products Regulatory Authority (SAHPRA) since then (Gqaleni *et al,* 2007), putting strain on an already overburdened system.

Clinical evidence for some of these herbal remedies' use lacks hard scientific data, and the efficacy of these remedies is rarely tested under controlled circumstances to elucidate the minimum effective dose, possible side effects and interactions (Meolie *et al,* 2005). Many claims are exaggerated, with minimal information on side effects or potential drug-CAM interactions (Morris & Avorn, 2003; Meolie *et al,* 2005; Owens, Bergens & Puckett, 2014). Fewer than 3 % of CAMs companies cite scientific literature on their websites and inserts

(Owens, Bergens & Puckett, 2014). Allopathic medicines are strictly regulated and controlled, from inception of the molecule to final registration. Use of complementary medicines is based on tradition, passed down through generations. Valerian Root, for example, has been used to treat anxiety and insomnia since at least the 18th century in Europe (Fernandez-San-Martin *et al,* 2010). If the current stringent requirements expected of allopathic medicines were applied to complementary medicines, few complementary medicines would fulfil the requirements for registration.

Complementary medicines are not regarded as food or nutritional supplements, and yet are also not fully regarded as medicines either. Numerous complementary medicines derived from plant extracts have a known pharmacological effect, and historically have been mankind's greatest source of medicine throughout the centuries. Aspirin, digoxin and opiates were all first plant-based medicines. Despite this, the current portfolio of complementary medicines is not subject to the same degree of scrutiny as allopathic medicines. Because the full pharmacological profile of plant-based complementary medicines is not known, it is imperative that what is known about the complementary medicine is presented to the patient in such a way that it can be understood.

1.1 Package Insert Requirements

Package Inserts (PIs) are intended to be the first point of information for clinicians and health care professionals (MCC Guideline 2.16 Package Inserts for Human use, 2013). The package insert is the document that ensures the safe and effective use of medicines under most circumstances (MCC Guideline 2.16 Package Inserts for Human use, 2013). The function of the package insert is to provide scientific and objective information regarding the use and safety of the medicine, as well as its limitations, as established by supporting evidence (MCC Guideline 2.16 Package Inserts for Human use, 2013). Companies may not use the PI or the PIL (Patient Information Leaflet) for promotional information (MCC Guideline 2.16 Package Inserts for Human use, 2013). No marketing or promotional claims may be made in the PI or PIL; only evidence from scientific studies or acceptable references may be included in this text to guide the healthcare professional and the patient in the correct use of the medicine.

Acceptable references to use to populate a Package Insert of a Complementary Medicine include recognised herbal pharmacopoeias or monographs, particularly if they are published by a stringent regulatory authority (for example, the EU, USA or Japan), or an authority with which the South African authority aligns itself, for example, the Canadian or Australian Health Authorities. The MCC Guideline on Package Inserts for Human use (2013) references other textbooks, such as the Goodman and Gilman, that are also accepted as references for the information included in a PI or PIL.

1.2 Patient Information Leaflet Requirements

The Regulations to Act 101 of 1965 require that every medicine has an accompanying Patient Information Leaflet (Regulations to Act 101 of 1965). The PIL must be constructed from the latest approved Package Insert (MCC Guideline 2.14 Patient Information Leaflets (PILs), 2013). The information contained within the Package Insert must be re-written in such a way that it is understandable to the patient with a non-medical background (WHO, 1999), MCC Guideline 2.14 Patient Information Leaflets (PILs), 2013). The South African regulatory requirements state that the PIL should not contain lengthy sentences, nor should the PIL contain abbreviations or terminology that a patient or non-medical person is unlikely to understand (MCC Guideline 2.14 Patient Information Leaflets (PILs), 2013).

While registered medicines are required according to Regulation 10 of Act 101 of 1965 to have both a PI and a PIL, complementary medicines should be complying to the same principle, the lack of compliance to the guidelines and regulations is worthy of research and questions around the population of the PI and PIL remain questionable.

1.3 Interpretation and understanding of medical text by non-medical people

Patient Information Leaflets (PILs) are intended to be read by a patient with no medical background or medical literacy. Therefore, the information must be delivered at an appropriate level. The PIL contains the information that a 'responsible' patient would need to know and is a lay person's version of the Package Insert (WHO, 1999). The information in a PIL for any complementary medicine should be written in a simple, unambiguous manner so that the patient is easily able to identify and remember the risks that may be involved in taking

a natural medicine. The PIL must be written in such a way that it does not cause confusion, nor overwhelm the patient with information.

One method of analysis for the interpretation of text, including the power differential within the text and the dynamics of the text, is Critical Discourse Analysis. Critical Discourse Analyses (CDA) is the critical study of language, with a specific focus on where power lies within the text. Power within a text is defined by who has knowledge and access to information, and who is ultimately disadvantaged by the text (Janks *et al*, 2014). This is effected by a lack of equality between the various parties involved in a particular discourse (Fairclough N., 1995); in this case, the author and the reader. One of the underlying ideas of Critical discourse analysis (CDA) is that no text is neutral; texts are influenced by the author's mind set and beliefs, and by the readers knowing, and not knowing certain concepts, ideas or terminology (Fairclough N., 1995; Janks *et al*, 2014). This imbalance in the text created by sociocultural contexts, by who has knowledge and access to particular information, gives the text power.

A study on patient attitudes and behaviour toward PIs and PILs found that only one out of four patients read the Patient Information Leaflet (Leemans *et al,* 2011). According to researchers, most patients skip straight to Dosage and Side Effects. As CAMs are available without prescription, many patients do not seek the advice of a health care professional, but rather take advice from less reputable sources such as family members, friends, colleagues and the internet. In fact, more than half of the respondents from the study conducted by Leemans *et al*, 2011) stated that they obtained most of their information from the internet.

As patients read the PI and PIL for safety information and dosage information (Leemans *et al,* 2011) it is imperative that the information in the inserts is provided in such a way that can be reasonably expected to be understood by a lay person with no medical background.

As complementary medicines can be purchased without any assistance or advice from qualified healthcare professionals, the patient has only got the insert in the carton to provide information on the products and decide whether a particular alternative therapy is appropriate for them.

With this in mind Critical discourse analysis is a useful analytic tool. It offers a way of deducing meaning through alternative interpretations of the text (Shaw and Bailey 2009). By unravelling assumptions and discursive practices, one can understand what certain assumptions may mean for other individuals (Shaw and Bailey 2009). Meaning from texts and any other discursive practice is derived from the reader's own personal points of view, their biases and assumptions. Critical discourse analysis provides a way of gaining insight into different potential meanings and interpretation.

1.4 Problem Statement

The PIs and PILs of complementary medicines are not controlled to the same degree as allopathic medicines with respect to their contents and the completeness of the information provided, although South African Law requires it. The language used in PIs and PILs are often medical in nature and exclude the patient who reads it from understanding the risks of the medicine.

Complementary medicines are available to the public with no restrictions. They contain plant extracts and sometimes other substances that have active components to treat illness and diseases. The PI and PIL are essential for the safe use of any medicine. The PI and PILs for allopathic medicines are evaluated according to a published standard and have strict requirements for the information contained therein, from the Schedule 0 paracetamol products to the S6 oxycodones and other opiate medicines. The exact status of the concentrated extract of the plant material is not governed and appears to be exempt from 'normal' regulatory processes and oversight. The product information in the form of PIs and PILs are not subjected to the same scrutiny as those of allopathic medicines.

1.5 Study aims and objectives

The aim of this research report is to evaluate the current compliance of the PIs and PILs of currently marketed products to the published guidelines and analyse the suitability of the text to the patient. This research report also aims to validate the information contained within the package inserts and compare the information presented in the PIs with the PI of the corresponding product.

Four products are evaluated in this research report. Two plant extract preparations were selected that are commonly used in the treatment and alleviation of mild anxiety and depression. Two products containing Valerian Root used as calming and sedative agents were selected, and two St John's wort products were selected, which claim to be effective in mild depression. There are no true reference products for Complementary medicines, so the two products with the same ingredients will be compared. Critical discourse analysis is used to analyse the patient information leaflets or Package Inserts and consider whether they have been written in a patient centric way, as the PIs and PILs is only information the patient has when they purchase the product.

The objectives of the research report are to:

1. Validate the compliance of the contents of the PI to the requirements described in the Guidelines published by the SAHPRA;
2. Compare the PI information of 2 brands containing Valerian Root and St John's wort;
3. Validate information contained in the PIs and PILs of the products from published reference resources, and;
4. Analyse the language used in relation to the intended reader, using Critical Discourse Analysis.

1.6 Literature review

1.6.1 Valerian Root

Valerian Root is used as a sleep aid and to relieve nervousness (Canadian Natural Health Product Monograph for *Valeriana officinalis*, 2008; and Marko, M. G. and Der Mardersian A., 2017). Doses of Valerian Root for the treatment of nervousness and sleepless range from 225 mg to 12 g (Bent *et al*, 2006; Canadian Natural Health Product Monograph for *Valeriana officinalis*, 2008; Fernandez-San-Martin *et al*, 2010; Marko, M. G. and Der Mardersian A., 2017). Valerian Root appears to have an influence on slow wave sleep latency, and have a positive impact on sleep structure, and has been recommended by researchers for the treatment of insomnia (Donath *et al*, 2000). The active compound of Valerian Root is valerenic acid, and acts a potentiator of $GABA_A$ receptors, thereby contributing to Valerian Roots' anxiolytic and sedative properties (Khoma *et al*, 2007; Becker *et al*, 2014). Futhermore, Valerian Root has been shown to inhibit the breakdown of GABA in the brain (Bent *et al*,2006;

Fernandez-San-Martin *et al,* 2010). The pharmacokinetics and pharmacodynamics of Valerian Root appear to be variable across different age groups and weight ranges, which could account for the variability of the effectiveness of Valerian Root as a sleep aid (Anderson *et al*,2010).

1.6.2 St John's wort

St John's Wort has been used since the time of the ancient Greeks, where it was described by Hippocrates, Pliny and Galen as a treatment against demonic possession (Woelk, 2000). Since then St John's wort extract and dried powder are used all over the world and are available over the counter and from online stores in South Africa. Today, the most common indication for the herb is mild depression.

The efficacy of St John's wort varies between no effect (Shelton *et al*,2001) and as effective as prescribed antidepressants (Woelk, 2000; van Gurp *et al*,2002; Linde, Berne and Kriston, 2008). There are two compounds within St John's wort to which the anti-depressant effect of the plant is ascribed: hypericin and hyperforin (Canadian Natural Health Product Monograph for *Hypericum perforatum*, 2009; Fasinu, Gurley and Walker, 2016; Fava *et al*, 2005). Hyperforin is thought to work synergistically with phytochemicals found in St John's wort and inhibits the reuptake of GABA, serotonin, dopamine and nor-adrenaline (Fasinu, Gurley and Walker, 2016; Marko, M. G. and Der Mardersian A., 2017). St John's wort has numerous recorded side effects due to its action on cytochrome P450 in the liver (Borelli & Izzo 2009; Tsai *et al,* 2012). In spite of the many recorded interactions, St John's wort is reported to have a good safety profile when taken in isolation (Woelk, 2000; Shelton *et al*,2001; van Gurp, 2002; Fava *et al,* 2005; Linde, Berner and Kriston, 2008 and Borelli & Izzo, 2009).

Chapter 2: Method

2.1 The data set

Complementary medicines do not have originator products as is seen in the field of allopathic medicine, so there is no true reference product. It is also common to find plant extracts combined with other ingredients, intended to enhance efficacy. The other ingredients can be other plant extracts, or vitamins or minerals.

The active ingredients chosen for this analysis were Valerian Root and St John's wort from the anti-anxiety and anti-depression market. These herbal medicines were selected as they are perceived to be useful, safe and effective for the symptomatic relief of anxiety and depression. Two branded products containing Valerian Root and two other branded products containing St John's wort were analysed in this research report.

Two products containing Valerian Root, namely Biral® Tablets (Appendix A) and Calmettes Nite tablets (Appendix B) were analysed. Biral® is a well-publicised name and a widely known over the counter tranquiliser containing Valerian Root. Calmettes Nite has similar ingredients and dose of Valerian Root compared to Biral®.

The two St John's wort brands selected were Flora Force St John's wort (Appendix C) and Wellvita St John's wort (Appendix D). Wellvita St John's wort was selected as it is one of the few St John's wort preparations that does not contain additional ingredients. Flora Force St John's wort was selected as it is a single ingredient formulation, available online and in health shops. A table of the products evaluated, and the information contained within the product packaging is summarised below:

Table 1: Summary of the types of information contained in study products

Product name	Package insert included	Patient Information Leaflet included
Biral®	✓	✓
Calmettes Nite	✓	
Wellvita St John's wort	✓	
Flora Force St John's wort	✓	

2.2 Data Collection

The package inserts were obtained from these products that are currently available in pharmacies and health shops. All products were found in the front shop. of the pharmacy and located without assistance from pharmacy staff. Because the products are available without having to request information or advice from pharmacy staff, patients are forced to rely on the PI and the PILs for information.

2.3 Data analysis

The methods described in this chapter were used to investigate the objectives described in Chapter 1.5 above. The methods used to analyse these texts was four-fold: (a) the package inserts were compared to the current SAHPRA requirements for a PI or PIL, (b) the information contained in the package inserts was compared between the two package inserts for the same active ingredient, (c) the information in the package inserts was compared to the results of online literature searches with respect to each of the headings of the package insert and (d) a Critical discourse analysis was conducted on the information intended for the patient. As PILs are written for the patient, this was analysed, however if no PIL was present, the PI was evaluated instead.

2.3.1 Objective 1: Compliance to Regulatory Guidelines

For the first phase of the analysis the package inserts were assessed according to each heading presented in the PI. The heading and the contents were compared to the requirements listed in the guidelines on Package Inserts published by the SAHPRA to determine whether the heading was included, and the information was written in the correct

format with the required wording. Compliance was assessed by a yes – no system: if the information was present, the PI received a green "Complies to the Guideline", a yellow "Partially complies to the Guideline" if the information was not fully presented as required in the Guideline, and a red "Not Compliant" if the information required was absent or did not comply to the Guideline at all. Data was recorded on a data collection sheet constructed from the guidelines per product (Appendix E). The information under each of the headings was colour coded.

2.3.2 Objective 2: Comparison of information between similar products

In the second phase of the analysis the information presented in each of the headings in the Biral® Tablets and Calmettes Nite tablets PIs was compared. This was repeated for the information contained in the Wellvita St John's wort and Flora Force St John's wort PIs. The information contained under each heading in both PIs were compared to find differences and similarities for each product with the same active ingredient and having similar indications.

2.3.3 Objective 3: Validation of information against published references

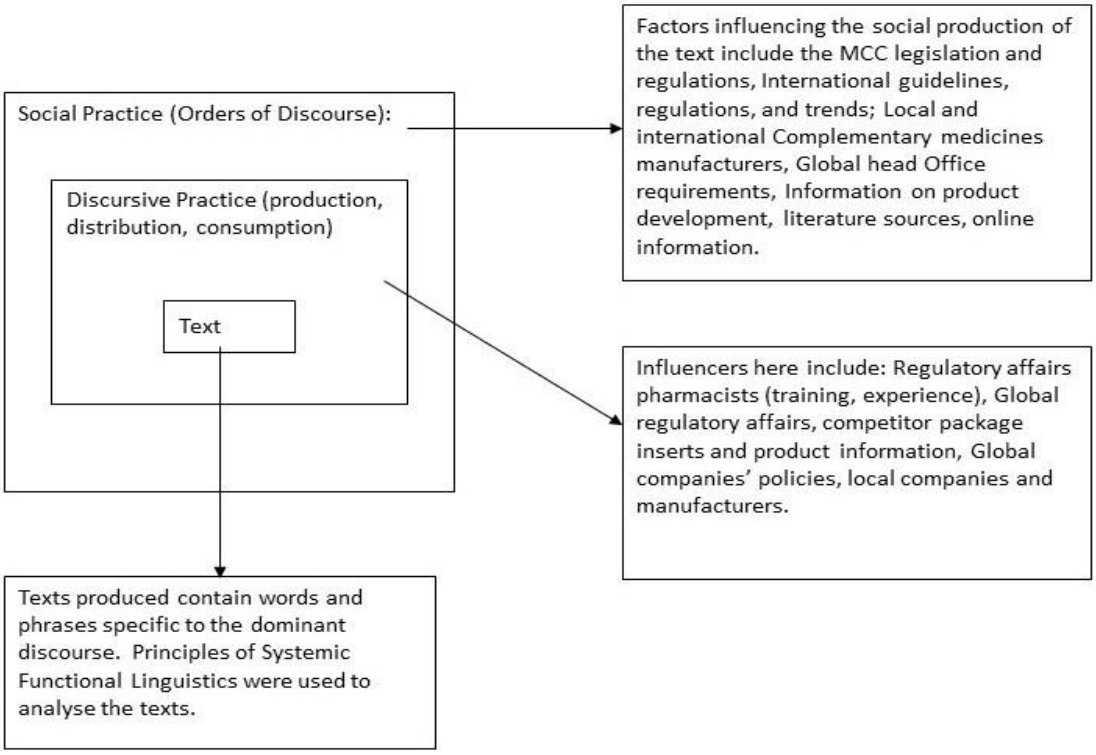
A literature search for each active ingredient and PI heading was performed in the third phase of analysis. Pubmed, The Cochrane Database, and the Canadian Herbal Pharmacopoeia were consulted for information. The Canadian Pharmacopoeia was used as the SAHPRA aligns with the Canadian Regulatory Authority on regulatory decisions, and a pharmacopoeia, published by the Canadian Health Authority is available for reference purposes. The literature reviews for Valerian Root and St John's wort are shown separately in the discussion.

2.3.4 Objective 4: Critical discourse analysis

Critical discourse analysis encourages the evaluator to understand the dynamic, fluid relationship between the text and its reader that defines the power balance between the two, and the social constructs that come about as a result of the language used (Janks *et al*. 2010). Critical discourse analysis examines the social effects of language, the creation of bias and distribution of power within a text, and who is included or excluded from reading a certain text (Janks & Dixon, 2014).

There are many different approaches that can be used to perform a critical discourse analysis, however the three-dimensional theoretical framework presented by Fairclough (1995, 2001) has been used in this analysis. This theoretical framework provides a platform for the examination of the various forces involved in the production of a text; namely the text itself, the actual production, distribution and consumption of the texts and the sociocultural analysis surrounding the text. The model can be represented as a series of interconnected boxes, all existing within each other, as depicted below:

Figure 1: Fairclough's Theoretical Model in relation to the analysis of the PI and PIL (Fairclough, 2001)



According to Fairclough (1995), CDA is performed through the analysis of text, the analysis of the text production, distribution and consumption, and the sociocultural analysis of the text.

In relation to Figure 1, the three boxes represent a process that culminates in the production of the PI and PIL. The sociocultural or Social Practice box influencing the generation of the text are factors outside the author's influence and is what the author of the text draws on for information and guidance on how to write the text (Fairclough, 2001). In this context, the

influencers include government regulations, both local and international, online resources, company policies and manufacturing documents. Fairclough (2001) refers to these influences as Social Practice, however in this research it refers to the Guidelines and current regulatory framework for the production of the PI and PILs. The second box, Discursive Practice, examines what influences the choices made by the author of the text on a more personal level (Fairclough, 1995, 2001). This includes the experience and training of the regulatory pharmacist or person writing the PI/PIL, competitor information and local company policies regarding the generation of the PI/PIL. Finally, the third box represents the text itself, as influenced by the outer two boxes, and reflects a combination of the above influencers (Fairclough, 2001). When critically analysing a text, the text is first 'deconstructed', and the re-construction of the text is systematically analysed, in order to answer the following questions: Who benefits from the text? Who is included, and who is excluded? What other ways of interpreting the text are there? Has bias been introduced? (Janks & Dixon 2014).

The information contained in each of the sections was also examined from a compliance perspective, and whether the information was objective and informative, yet still written in a way that does not exclude the layman reader.

The PI is the more scientific and explanatory piece of information contained within the product packaging, so this will be evaluated against the Guidelines for compliance and will be validated through searches in published literature. The PIL is constructed from the PI (Guideline 2.14 and 2.16, 2013), therefore the information in the two pieces of texts should be the same. The PIL is written for the patient so this will be analysed according to the principles of discourse analysis to gain an insight into what a patient may understand. If a PIL has not been provided in the product packaging, the PI will have to be analysed, as this is all a patient can read for information. Where there is a difference in the information between the PI and the PIL, the PI will be brought into the CDA analysis.

Chapter 3: Results

The package inserts for Biral® and Calmettes Nite tablets, both containing similar amounts of Valerian Root, are presented in tables below, comparing the contents appearing under each heading in each of the package inserts. The St John's wort products, Wellvita St John's wort and Flora Force St John's wort are similarly compared in the second part of the results chapter. The contents of the similar products are compared to each other and the requirements of the MCC's guideline for Package Inserts for Human use (2013) and the Patient Information Leaflet (2013), as applicable to the literature contained within the product pack. An analysis of the language used in the construction of the package inserts according to the principles of critical discourse analysis follows each section. The literature findings of Valerian Root and St John's wort are discussed in chapter four.

3.1 Valerian Root

Biral® and Calmettes Nites package inserts (PI) are compared in the table below (Table 2). The content under each heading is compared to the requirements of the guidelines using the data collection sheet (Appendix E), and then to each other PI to see where similarities and differences lie. A discussion of the areas of compliance and non-compliance follows. The literature review of Valerian Root follows in the Chapter on Discussion.

Table 2: The comparison of Package Insert (PI) completeness for two Valerian Root containing products

PI Heading	**Biral® Tablets Package Insert**	**Calmettes Nite Tablets Package Insert**
(MCC Guideline 2.16 Package Inserts for Human use, 2013)	**Biral® Tablets** **Compliant to Guidelines**	**Calmettes Nite Tablets** **Compliant to Guidelines**
Scheduling Status (MCC Guideline 2.16 Package Inserts for Human use, 2013)	S0 **Compliant to Guidelines (old medicine)**	Not Scheduled **Compliant to Guidelines**
Proprietary Name and Dosage Form (MCC Guideline 2.16 Package Inserts for Human use, 2013)	**Biral®** sugar coated tablets. **Compliant to Guidelines**	**CALMETTES NITE TABLETS** **Compliant to Guidelines**
Composition (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Each tablet contains: *Valerianae extractum siccum* 100 mg *Passiflorae extractum siccum* 45,0 mg **Contains sugar** **Partially compliant to Guidelines**	Each coated tablet contains: 125 mg Valerian root dry extract (3-6:1, ethanol 70% % v/v), equivalent to 375 – 750 mg Valerian root (extract of plant root *Valeriana officinalis*). **Partially compliant to Guidelines**
Pharmacological classification (MCC Guideline 2.16 Package Inserts for Human use, 2013)	A 2.6 Tranquilisers **Compliant to Guidelines**	A.34 Herbals **Compliant to Guidelines**
Pharmacological Action / Pharmacodynamic properties / Pharmacokinetic properties	Valerian and Passiflora are natural products of plant origin, which act on the central nervous system to bring about a mild sedative action.	**Pharmacodynamic properties** In clinical studies in patients with sleep disturbances, Valarian root extract has shown to improve sleep efficiency and quality, predominantly by shortening the sleep latency and increasing the slow wave sleep proportion. Subjective sleep parameters, as assessed by means of self-rating scored and questionnaires, improved accordingly.

PI Heading	Biral® Tablets Package Insert	Calmettes Nite Tablets Package Insert
(MCC Guideline 2.16 Package Inserts for Human use, 2013)	**Compliant to Guidelines**	Valerian had no immediate hypnotic effect but rather restored sleep macrostructure. In insomniac patients, the therapeutic benefit could be observed in the first days of treatment and further increased within the next 2-4 weeks. Furthermore, clinical studies have demonstrated that Valerian treatment relieved symptoms of nervousness and restlessness. Frequently associated problems like deficiencies in the concentration ability and motor restlessness are markedly improved in adults and children. **Pharmacokinetic properties** No human data on absorption, distribution, metabolism and excretion are available in the literature, and no pharmacokinetic studies have been performed on extract of Valerian root. However, the observed clinical efficacy and the toxicological studies have shown indicate absorption and suggest that neither toxic metabolites are formed nor toxic constituents of the extract accumulate. **Compliant to Guidelines**
Indications (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Anxiety, restlessness and minor neuroses characterised by the absence of depression. **Compliant to Guidelines**	Calmettes Nite is a herbal medicinal product indicated for the relief of temporary mild nervous tension and temporary difficulty in falling asleep. **Compliant to Guidelines**
Contra-indications (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Hypersensitivity to the ingredients. There are no known contra-indications. **Compliant to Guidelines**	Not recommended for patients with hypersensitivity or idiosyncrasy to root of valerian or any of the excipients **Compliant to Guidelines**
Warnings and Special Precautions (MCC Guideline 2.16 Package Inserts for Human use, 2013)	**Not Compliant**	**Partially compliant to Guidelines (included below)**
Interactions (MCC Guideline 2.16 Package Inserts for Human use, 2013)	No known interactions **Compliant to Guidelines**	**Partially compliant to Guidelines (included below)**

PI Heading	Biral® Tablets Package Insert	Calmettes Nite Tablets Package Insert
Pregnancy and Lactation (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Safety during pregnancy and lactation has not been established. **Compliant to Guidelines**	**Partially compliant to Guidelines (included below)**
Dosage and Directions for use (MCC Guideline 2.16 Package Inserts for Human use, 2013)	*Adults*: Unless otherwise directed, initially two tablets should be taken with water three times daily after meals. After improvement or in less severe case, one tablet should be taken three times daily after meals. **Compliant to Guidelines**	**Adults and children over 12 years of age** As an aid to sleep, a single oral dose of 3-5 coated tablets (equivalent to 1125-3750 mg valerian root) half an hour before bedtime, with an earlier dose during the evening, if necessary. For relief of nervous tension, a single oral dose of 3-5 coated (equivalent to 1125 – 3750 mg valerian root) 1-3 times daily. **Elderly** As for adults. The coated tablets should be swallowed with fluids and not be chewed. **Compliant to Guidelines**
Side Effects (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Adverse reactions with normal therapeutic doses are unknown. Should any adverse reaction occur; discontinue medication immediately. **Compliant to Guidelines**	No adverse effect is known to date under the recommended conditions of use. **Precautions** Since only limited clinical experience is available, the use of Calmettes Nite in children younger than 12 years of age is not recommended. As it may enhance the central nervous depressing effects of alcohol, hypnotic, anxiolytic, narcotic, sedative and tranquilising agents, CALMETTES NITE should be used with caution when co-administered with these agents. CALMETTES NITE should be used with caution in patients with a history of severe liver dysfunction or sever liver disease. Since data on the use during pregnancy and lactation are not available, the use of CALMETTES NITE is not recommended as a general precaution. Intake of CALMETTES NITE immediately (up to two hours) before driving a car or operating machinery is not recommended. **Compliant to Guidelines**
Known Symptoms of Overdose and	Overdose or prolonged use should not give rise to any toxic effects. However, should any severe symptoms occur	Valerian root at a dose of approximately 20 g caused mild symptoms (fatigue, abdominal cramp, chest tightness, lightheadedness, hand tremor and mydriasis)

PI Heading	Biral® Tablets Package Insert	Calmettes Nite Tablets Package Insert
Particulars of Treatment (MCC Guideline 2.16 Package Inserts for Human use, 2013)	following overdose, consult a medical practitioner or nearest hospital immediately. **Compliant to Guidelines**	which disappeared within 24 hours. If symptoms arise, treatment should be supportive. **Compliant to Guidelines**
Identification (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Pale pink sugar-coated tablets. **Compliant to Guidelines**	White, round, biconvex coated tablet. **Compliant to Guidelines**
Presentation (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Available in blister strips, packed in cartons of 20, 40 and 100 tablets **Compliant to Guidelines**	PVC/PVDC blister strips in cartons of 25 coated tablets. **Compliant to Guidelines**
Storage instructions (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Store in a cool, dry place. Store at or below 25 °C. Store out of reach of children **Compliant to Guidelines**	Store below 25 °C, in a dry place. KEEP OUT OF REACH OF CHILDREN. **Compliant to Guidelines**
Registration Number (MCC Guideline 2.16 Package Inserts for Human use, 2013)	B1503 (Act 101/1965). **Compliant to Guidelines**	**Not necessary as product is not scheduled**
Name and Business Address of the Holder of the Certificate of Registration (MCC Guideline 2.16 Package Inserts for Human use, 2013)	1 Libertas Road Cnr. Main Road and Sloane Street Bryanston, 2191 **Compliant to Guidelines**	Abbott Laboratories S.A. (Pty) Ltd 219 Golf Club Terrace Constantia Kloof 1709 **Compliant to Guidelines**
Date of Publication of the Package Insert	09 December 2008	25 April 2004

PI Heading	Biral® Tablets Package Insert	Calmettes Nite Tablets Package Insert
(MCC Guideline 2.16 Package Inserts for Human use, 2013)	**Compliant to Guidelines**	**Compliant to Guidelines**

Biral® contains a Patient Information Leaflet (PIL), whereas Calmettes Nite is neither compliant to the latest regulations, nor does it contain a Patient information leaflet (PIL). Non-compliance to the latest regulations is demonstrated by the missing headings: Warning and Special Precautions; Interactions; Pregnancy and Lactation.

In South Africa, the originator product, Biral® has been on the market before medicines were regulated as indicated by the old medicine registration number on the Package Insert. Medicines that were on the market before the Medicines and Related Substances Control was promulgated in 1965 were registered as Old Medicines (Act 101 of 1965). Since then the laws have been clarified and expanded, as have the definitions for Complementary and Alternative medicines. In order for a scheduling status to be assigned, the product dossier must be evaluated by the Naming and Scheduling committee of the SAHPRA, who will approve a particular schedule for the product. Calmettes Nite is also not a scheduled medicine and is classified as a complementary medicine.

Medicines are categorized into A, B and C medicines. Category A medicines are medicines for human use, Category B medicines denote medicines that cannot be administered without further manipulation, and Category C medicines is intended for veterinary medicines. When the Complementary medicines were first called up for registration, the Minister of Health created Category D medicines for human and veterinary medicines (Regulations to Act 101 of 1965, 2017(as amended)). Before the additional classification was gazette, Complementary Medicines for Human Use was assigned to Category A. The Biral PI was updated and published in 2008, and Calmettes Nite tablets PI was published in 2004, before the inclusion of the category D classification, so the 'A' classification appearing on both PI's was correct at the time of print. When the Calmettes Nite tablets PI is updated, the category will change. If Biral tablets are called to submit a new dossier for evaluation, this will also change to the current classification.

When evaluating the Package inserts (PI) it is clear that both PIs are compliant to the same heading required by the guidelines, namely: Proprietary Name and Dosage Form, Pharmacological classification, Indications, Contra-indications, Dosage and Directions for use, Side Effects, Known Symptoms of Overdose and Particulars of Treatment, Identification,

Presentation, Storage instructions, Registration Number and Name and Business Address of the Holder of the Certificate of Registration. The most immediately noticeable difference seen is in the length and content of the pharmacodynamics section in the Biral® and Calmettes Nite inserts. Calmettes Nite is significantly longer than Biral® with a word count of 170 words in the Pharmacodynamics sections of the Calmettes Nite insert, compared to 23 words in the Pharmacological Action section of the Biral® insert.

Neither insert addresses warnings or special precautions, and the Calmettes Nite PI has not included the sections for Interactions and Pregnancy and Lactation, although these sections have been addressed under Side Effects. While the information is present, it is not compliant with the current guidelines. These sections are important as they inform the reader about the safety of this medicine.

Biral® PI makes no mention of use in children or the elderly. Calmettes Nite mentions people who have liver disease should use the product with caution. Biral® does not mention the concomitant use of alcohol and other central nervous system (CNS) depressants, while Calmettes Nite package insert cautions the use of these medicines together with central nervous system depressants.

Calmettes Nite PI provides an extraction ratio, as well as the equivalent amount of root, so the patient is aware of how just how much they are taking, and that the tablet, and that the tablet, and that the tablet contains a concentrated extract. In contrast, the Biral® insert only gives the amount of Valerian Root in the tablet, with no indication of the extraction method or how concentrated the extract is. The European Union Monograph for Valerian Root recommends an ethanolic extract of 3-7,4:1 in 40-70 % ethanol for traditional and well-established uses of the plant root (EU herbal monograph on *Valeriana Officianalis L.,* radix, 2015).

Both Biral® and Calmettes Nite PIs contained the same information, with the exception of the indication for insomnia in Biral®, even though the PI does refer to its sedative and tranquilising properties. Both package inserts (PI) only partially comply with the requirements for the

Composition, as manufacturers are required to list all ingredients, including the inactive components of the tablets.

3.1.1 Critical Discourse Analysis

3.1.1.1 Critical discourse analysis of the Biral® PIL

The Biral® PIL uses short, unambiguous sentences, and includes the recommended text from the Guideline on PILs. This same wording used in the PILs of allopathic medicines. The first words the patient reads as they turn from the scientific PI to the PIL are the following words:

WHAT YOU NEED TO KNOW ABOUT Biral®

- Please read this leaflet carefully before you start using this medicine.
- Keep this leaflet with your medicine as you may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

The language in this section is unambiguous and informs the patient what to expect from this leaflet, as well as the instructions "Keep this leaflet with your medicines as you may need to read it again" and refers the patient to their doctor or pharmacist if they have more questions.

WHAT Biral® CONTAINS

Each **Biral®** sugar coated tablet contains:

Dry extract of Valerian	100,0 mg
Dry extract of Passion Flower (Passiflora)	45,0 mg

Other ingredients:

Lactose, croscarmellose sodium, polyvidone, magnesium stearate, microscrystalline cellulose, methylhydroxypropyl cellulose, silicon defoaming emulsion SE2-MC, sucrose, calcium carbonate, talc, colloidal silicon dioxide, acacia, titanium dioxide, iron oxide black, iron oxide yellow, iron oxide red, beeswax, carnauba wax.

The first heading: "What Biral® Contains" informs the patient of what is in the tablet, but the patient is not informed what the active ingredients are, and what the inactive ingredients are. The SAHPRA guideline on Human Package inserts (PI) and the guideline on Patient information leaflet (PIL)s requires all inactive ingredients to be listed, but nowhere in the insert is the patient informed that these ingredients are only fillers used to make up a tablet. This information on the inactive ingredients would also be better placed in the PI. The dry extract of Valerian Root is the active ingredient, but not all patients will be aware that this is the

active ingredient. The extraction ratio and solvent have also not been listed, as is required by the E.U. monograph on *Valeriana Officianalis L*., radix (2015).

WHAT Biral® IS USED FOR
Valerian and Passiflora are natural products of plant origin, which act on the central nervous system to bring about a mild sedative action.

The use of the word natural is connected to the noun plants. Natural is a loaded signifier and may be associated with ideas of harmlessness and has no chemical additives. This is reinforced by the word 'mild' – it is implied that the effects of the product are gentle on the system. The use of the technical term sedative potentially hides the fact that this is a tranquilliser. Combining these terms may confuse the patient, as natural products imply organic pureness and are perceived to be safer and less toxic than allopathic medicines.

The use of the word "sedative" is not appropriate language for a PIL as it may be confusing to patients or non-medical consumers, as this word is one most commonly used when referring to anaesthesia or prescription medicines used for sleeping and panic attacks. The Merriam-Webster online medical dictionary defines a sedative as sedative agent or drug, and tending to calm, moderate or tranquilize (Merriam-Webster, 2003). The word 'calming' in this context would be a more appropriate term.

The indication in the Biral PI is different to what has been included in the PIL. The PI states that Biral is indicated for: "Anxiety, restlessness and minor neuroses characterised by the absence of depression". The term 'anxiety' has changed its meaning over the years, from the Freudian definition of impending danger based on neuroses (Boeree, C. G., 2009) to the comprehensive definitions we have today on anxiety, now recognised as a psychiatric disorder. Anxiety is now one of the most common diagnoses in psychiatry and general medicine (Kupfer D., 2015). The DSM-5 has expanded the definition of anxiety, allowing for a more holistic approach to the diagnosis and treatment of anxiety (Kupfer D., 2015). Generalised Anxiety Disorder (GAD) is now defined by the DSM-5 as excessive anxiety and worry which is difficult to control, and associated with the following symptoms: restlessness, fatigue, sleep disturbance, difficulty concentrating, irritability and muscle tension (American Psychiatric Association, 2013). The indication in the PI not only mentions anxiety, but also

lists restlessness, a diagnostic criterion for anxiety, and is indicated as a sedative for sleep disturbances. Patients suffering from the symptoms of GAD should be assessed by a doctor for the severity of their symptoms, however the Biral PI and PIL has positioned itself as a natural and safe treatment for anxiety. Patients suffering from GAD will identify with the indications in the PI and the PIL, the efficacy of which will be discussed in chapter 4.

If you are taking other medicines on a regular basis, the use of this medicine as well may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice.
If you are pregnant or breastfeeding a baby please consult your doctor, pharmacist or other health care professional for advice before taking this medicine.

The text above is boxed on the PIL and is in bold lettering as required by the Guideline on Patient information leaflet (PIL)s. It clearly tells the patient to disclose all other medicines to their doctor or pharmacist *before they take the product*. However, the only text included by the pharmaceutical company is a warning not to use this if one is allergic to the ingredients. There are no warnings regarding the use of this product with alcohol or other central nervous system depressants, which was included in the Calmettes Nite PI. This section, even though it must be included, conflicts with the previous section about the natural product of plant origin, as well as with the PI, which states there are no known interactions. The patient is first told this is a 'mild', natural product, then this section refers to this product as a medicine that may have interactions. The PIL presents conflicting messages that leave the patient confused as to what the medicine is, and what it does.

The irony of these required sentences is that this product is available to buy off the shelf, without having to speak to their doctor or pharmacist. Some of the reasons that have been identified as to why patients avoid seeking professional medical advice include:

a) unfavourable evaluations or perceptions of the medical care received from doctors and healthcare organisations (Taber *et al*, 2014);
b) low perceived need to seek out medical advice or care as the patient believes the problem will go away on its own and medical intervention is unnecessary (Taber *et al*, 2014) and;
c) traditional reasons such financial constraints or a lack of medical aid (Taber *et al*, 2014)

In the South African setting, doctors are expensive, clinics are poorly run, pharmacies are busy, and the patient may simply be too shy to get speak to a professional, so the chances of the patient asking for advice are slim.

The Patient information leaflet (PIL) tells the patient to take Biral® tablets as follows:

HOW TO TAKE Biral®
Adults: Unless otherwise directed, initially two tablets should be taken with water three times daily after meals. After improvement or in less severe cases, one tablet should be taken three times daily after meals.

The passive tense of the PIL gives the patient control over the dosage, and allows the patient to decide what will be effective. The active voice would provide the patient with a clearer instruction: Take two tablets three times daily. The passive allows the patient to decide what dose is appropriate or sufficient. The patient can then also decide when their unspecified condition is less severe to reduce the dosage. The passive style of writing leaves the sentence open to interpretation, and creates vague, ill-defined situations about when dosage should be adjusted.

SIDE EFFECTS
Adverse reactions with normal therapeutic doses are unknown. Should any adverse reactions occur discontinue medication immediately. Hypersensitivity has been known to occur with dry extract of Passion Flower (Passiflora).

Not all side effects reported for this medicine are included in this leaflet. If your general state of health worsens while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.

More medical terminology has been used in this section than in previous sections. Words like “adverse reactions”, “therapeutic doses” and “hypersensitivity” are not patient friendly and are unlikely to be used in everyday discourse. The meaning of the word “unknown” in this context is not clear. It is not clear whether unknown means that the company does not know about any side effects of Biral®, or whether side effects never occur with Biral®.

The phrase “If your general state of health worsens” is very vague and gives the patient no guidance on how to interpret the instruction. An adverse reaction also includes the product not working as it should and does not only refer to symptoms of side effects. Anxiety is a

clinical disorder with severe consequences if not treated correctly. If symptoms of anxiety worsen the patient should seek medical attention, however this is not explained.

There is no description about the kind of hypersensitivity that has been reported with Passion Flower. Hypersensitivity can take on different forms with different levels of severity. A lay person will not know what this looks like in order to stop the medication, and the PIL provides no guidance. The disclaimer that not all side effects may be listed also leaves the onus on the patient to make the decision as to the risks of the medicine. The company has protected itself with this wording, but the patient may misinterpret this section. The natural product of plant origin referred to in earlier sections is now referred to as "medication"' and "medicine". Medicine is a scientific term, and implies there is research behind the product, with valid results.

3.1.1.2 Critical discourse analysis of the Calmettes Nite PI

The Calmettes Nite insert uses more medical jargon and pharmacological terms than the Biral® PIL. As demonstrated with Biral®, the company protects themselves, at the expense of the patient. This is particularly relevant here, where only a Package Insert is available for an off the shelf, non-scheduled medicine.

Each coated tablet contains:
125 mg Valerian root dry extract (3-6:1, ethanol 70% v/v), equivalent to 375 – 750 mg Valerian root (extract of plant root *Valeriana officinalis*).

The Calmettes Nite PI begins with the composition of the product in milligrams, followed by the active ingredient and then a dilution ratio in parenthesis, none of which would be understood or hold any meaning to a patient. By comparison, the Biral® PIL places the active ingredient name first, and the quantity second. Calmettes Nite contains 25 mg extra valerian compared to the Biral® product, so for a patient making a decision based on comparison, this may sway their purchase to the Calmettes Nite product as it is 'stronger' based on active ingredient content.

Pharmacodynamic properties
In clinical studies in patients with sleep disturbances, Valerian root extract has shown to improve sleep efficiency and quality, predominantly by shortening the sleep latency and increasing the slow wave sleep proportion. Subjective sleep parameters, as assessed by means of self-rating scored and questionnaires, improved accordingly.
Valerian had no immediate hypnotic effect but rather restored sleep macrostructure. In insomniac patients, the therapeutic benefit could be observed in the first days of treatment and further increased within the next 2-4 weeks.

Furthermore, clinical studies have demonstrated that Valerian treatment relieved symptoms of nervousness and restlessness. Frequently associated problems like deficiencies in the concentration ability and motor restlessness are markedly improved in adults and children.

Calmettes Nite has two sections on pharmacodynamics and pharmacokinetic properties of the valerian root compared to Biral® which contained only a brief statement on the effect of the root on the central nervous system. Neither of the sections in the Calmettes Nite PI was written for a layperson; they both reference clinical studies and use very technical medical terminology: “sleep latency”, “slow wave sleep proportion”, “hypnotic effect”, “sleep macrostructure”. Highly technical terms such as these are likely to intimidate the non-medical reader. The result is that they may stop reading as they do not understand the subject matter. While one can argue this is intended as professional information, the lack of any other patient information means this is all a patient can use to base their decision whether to buy this medicine.

Calmettes Nite appears to be trying to position itself as a clinical, organic equivalent to well-known anti-anxiety medicines like benzodiazepines. The inclusion of clinical studies may have been done in an effort to persuade either the doctor or patient that this product has sound scientific background research supporting it. The terms “clinical studies” have been mentioned twice in the pharmacodynamics section. The last sentence under pharmacodynamics has an additional indication, “Frequently associated problems like deficiencies in the concentration ability and motor restlessness are markedly improved in adults and children”. This is not mentioned anywhere else on the PI and is not a registered indication for Valerian Root, yet it has been included in the pharmacodynamics section through the mention of clinical studies. This could be a marketing strategy to doctors, or even the consumer who reads all the package inserts (PI).

Pharmacokinetic properties
No human data on absorption, distribution, metabolism and excretion are available in the literature, and no pharmacokinetic studies have been performed on extract of Valerian root. However, the observed clinical efficacy and the toxicological studies have shown indicate absorption and suggest that neither toxic metabolites are formed nor toxic constituents of the extract accumulate.

In comparison to the pharmacodynamics section above, the pharmacokinetics section pleads a lack of clinical data. The company has said there is no clinical data, yet they present information on the clinical efficacy and toxicological studies showing absorption and metabolism. Specific reference to clinical studies in the above section bears witness to the efficacy of Valerian Root, however no studies are mentioned in this section, with only observations making reference to the lack of toxicity or toxic metabolites. These inconsistencies within the PI create tension and confusion for the reader; there must be pharmacokinetic data for the company to make these statements, but have disregarded this data, possibly to present the product as safe. The heading of this section requires a knowledgeable reader and the large amount of jargon again potentially discourages lay people from progressing any further and connecting with the information.

The Indications sections is the first section a patient or consumer could be expected to read and understand within the package insert.

INDICATIONS
Calmettes Nite is a herbal medicinal product indicated for the relief of temporary mild nervous tension and temporary difficulty in falling asleep.

The terms “herbal medicinal product” are likely to be understood by a non-medical person. By combining these two words, the company does the same as the Biral® PIL and creates the idea that this is a natural product, effective for short term anxiety and insomnia. Biral® uses ‘mild’ in the same section of their PIL, and confirms that this product itself is mild, as it is linked to nature, and is free of harmful chemicals. Mild and temporary are also relative terms, which has different meanings to different people. Both mild and temporary can therefore mean a range of experiences and allows the patient to decide how and when to use the product.

CONTRA-INDICATIONS

Not recommended for patients with hypersensitivity or idiosyncrasy to root of valerian or any of the excipients.

The terms "hypersensitivity", "excipients" and "idiosyncrasy" are not patient friendly information and have not been explained anywhere in this insert. The active ingredient is written as "root of valerian", compared to previous sections where it is referred to as Valerian Root. The PI warns patients not to take the product if they are allergic to any of the excipients, however none of the excipients have been listed under Composition. The use of these technical terms and passive voice for the active ingredient discourages the reader from completing this section. The fact that this occurs in the contra-indications is no coincidence. The company is protecting itself by including this statement, even though a patient is not likely to understand this section.

DOSAGE AND DIRECTIONS FOR USE

Adults and children over 12 years of age

As an aid to sleep, a single oral dose of 3-5 coated tablets (equivalent to 1125-3750 mg valerian root) half an hour before bedtime, with an earlier dose during the evening, if necessary.

For relief of nervous tension, a single oral dose of 3-5 coated (equivalent to 1125 – 3750 mg valerian root) 1-3 times daily.

Elderly

As for adults.

The coated tablets should be swallowed with fluids and not be chewed.

Calmettes Nite seems to provide the patient with a simple instruction, however the use of parenthesis with the raw root equivalent dose does not provide meaning to the patient and may have the opposite effect. The patient may panic at the thought of taking 5 tablets at a time, and high dosage equivalent may prevent a patient from taking the product appropriately. They further go on to say an earlier dose may be taken, but do not specify how much earlier, and what qualifies as "necessary". This lack of clarity can easily lead to an overdose, by taking 5 tablets at an 'earlier' time, and another 5 before bed. There is no guidance on the dosing interval, or how much earlier the patient can a dose, again, causing confusion and tension within the text.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

No adverse effect is known to date under the recommended conditions of use.

Precautions

Since only limited clinical experience is available, the use of Calmettes Nite in children younger than 12 years of age is not recommended.

As it may enhance the central nervous depressing effects of alcohol, hypnotic, anxiolytic, narcotic, sedative and tranquilising agents, CALMETTES NITE should be used with caution when co-administered with these agents.

CALMETTES NITE should be used with caution in patients with a history of severe liver dysfunction or severe liver disease.

Since data on the use during pregnancy and lactation are not available, the use of CALMETTES NITE is not recommended as a general precaution.

Intake of CALMETTES NITE immediately (up to two hours) before driving a car or operating machinery is not recommended.

Calmettes Nite also refers to a 'recommended dose'. The recommended dose is not clearly described in the last section, similarly to what was observed in the Biral® PIL. There is no clarity whether taking the highest possible dose will have an effect on driving a car or operating machinery within the mentioned time frame of up to two hours. The inclusion of the words 'to date' makes the product sound safe but begs the question as to what may have been left out. If there are no known adverse effects to date this this raises the question as to when the last time this PI was updated.

Certain vulnerable populations have been excluded from using this product e.g. children and people driving cars and machinery yet have declared that there are no adverse effects. This section serves the interests of the company to protect them from litigation. Use of Valerian Root is also excluded with the concomitant use of benzodiazepines, narcotics and other central nervous system depressants (Canadian Natural Health Product Monograph for *Valeriana officinalis*, 2008), yet these were not contraindicated in the above sections.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Valerian root at a dose of approximately 20 g caused mild symptoms (fatigue, abdominal cramp, chest tightness, lightheadedness, hand tremor and mydriasis) which disappeared within 24 hours. If symptoms arise, treatment should be supportive.

Calmettes Nite begins this section on 'Known Symptoms of Overdose' with medical jargon and confusing terminology for a patient. Words like "fatigue", "lightheadness" and "mydriasis" are not patient friendly terms, and prevents the patient from reading and understanding this section, which contains important information for understanding when

this medicine is not appropriate. “Fatigue” and “lightheadedness” are also subjective terms, with different interpretations possible for different people.

Until this section, every time Valerian Root has been mentioned the equivalent raw root dosage has been included. Now it is unclear whether this dose refers to the extract form of Valerian Root (160 tablets containing 125 mg of valerian extract per tablet) or the equivalent dosage of the root (27 tablets containing approximately 750 mg plant root per tablet). This is not clear even for a healthcare professional. If a patient had to overdose, the listed symptoms are not written in a way that the patient could understand. Once again, the company has protected itself at the expense of the patient. The information is included in the PI; however, it is easy for a patient to misinterpret it, or not read it at all.

3.2 St John’s Wort

Both the Wellvita St John’s wort and the Flora Force St John’s wort only provide a Package Insert, which have been evaluated in table 3 below. The contents of each PI has been compared to each under each of the headings required by the MCC’s Guideline on PIs for Human Use (2013) and evaluated for compliance. The discourse analysis follows the discussion on the compliance to the Guidelines published by the MCC for PIs (2013).

Table 3: The comparison of Package Insert (PI) completeness for two St John's wort containing products.

PI Heading	Wellvita St John's wort Package Insert	Flora Force St John's Wort Package Insert
Scheduling Status (MCC Guideline 2.16 Package Inserts for Human use, 2013)	S0 **Compliant to Guidelines**	C0 **Not Compliant**
Proprietary Name and Dosage Form (MCC Guideline 2.16 Package Inserts for Human use, 2013)	St. JOHN'S WORT (capsule) **Compliant to Guidelines**	Flora Force St John's wort Capsules 300 mg **Compliant to Guidelines**
Composition (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Each capsule contains: Active ingredients: St. John's Wort powder *(Hypericum perforatum)* 300 mg and St. John's Wort extract (*Hypericum perforatum*) [hypericin 0,3 %] 175 mg. *Capsules are free of gluten, preservatives, sugar and lactose. **Partially compliant to Guidelines**	Each capsule contains Hypericum perforatum powder 300 mg. **Partially compliant to Guidelines**
Pharmacological classification (MCC Guideline 2.16 Package Inserts for Human use, 2013)	D 32.2 Other. Discipline: Western herbal. **Compliant to Guidelines**	Category D Western Herbal Medicine **Compliant to Guidelines**
Pharmacological Action / Pharmacodynamic properties / Pharmacokinetic properties	**Not Compliant**	1.2 Central nervous system Stimulants, psycho-analeptics (antidepressants). **Not Compliant**

PI Heading	Wellvita St John's wort Package Insert	Flora Force St John's Wort Package Insert
(MCC Guideline 2.16 Package Inserts for Human use, 2013)		
Indications (MCC Guideline 2.16 Package Inserts for Human use, 2013)	This product is used to relieve a slightly low mood and mild anxiety. This is based on traditional use only. **Compliant to Guidelines**	Herbal medicine for the treatment of anxiety, nervous stress and mild depression. **Compliant to Guidelines**
Contra-indications (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Do not use this use in medicine if you are hypersensitive (allergic) to any of the ingredients in the formula on; or if you are pregnant or breastfeeding. Not suitable for use in children under the age of 18 years, or for longer than one year continuously, unless under medical supervision. Avoid use in patients with Alzheimers disease or any mental illness. **Compliant to Guidelines**	Do not use with MOA inhibiting, or SSRI drugs and oral contraceptives, theophylline, simvastatin, and anti-histamine. Do not use when pregnant or breastfeeding. **Compliant to Guidelines**
Warnings and Special Precautions (MCC Guideline 2.16 Package Inserts for Human use, 2013)	If you suffer from any serious ailments or conditions; or if you are taking any prescribed medication, please check with your healthcare provider before taking this medicine. • This medicine might slow blood clotting and should be used cautiously with any other blood thinning medication. Discontinue use two weeks prior to any scheduled surgery. • Use cautiously if you have sensitive skin as this medicine might cause photosensitivity. Sunblock should be applied while taking this medicine. • Do not suddenly stop taking this medicine, the dosage should be decreased over a period of me. Please consult your healthcare provider for further advice. • This medicine can cause dizziness and can influence your ability to drive and use machines. Please exercise care when driving or operating machinery until you know how it affects you. • Porphyria: Safety has not been established. Nutritional supplements on should not replace a balanced diet. Do not exceed the recommended dose without consulting a healthcare provider. **Compliant to Guidelines**	Discontinue use 3 days before any general anaesthetic and surgery. Photo-sensitivity, avoid any exposure to ultra-violet lights and full sun. Persons on SSRI drugs should not take St John's wort (*Hypericum perforatum*). Discuss with medical practitioner. **Compliant to Guidelines**

PI Heading	Wellvita St John's wort Package Insert	Flora Force St John's Wort Package Insert
Interactions (MCC Guideline 2.16 Package Inserts for Human use, 2013)	If you are taking other medicines regularly, including complementary or traditional medicines, or start taking any additional medicines while taking this medicine, consult your healthcare provider for advice. This medicine may interfere with the way the body processes certain drugs using the liver's 'cytochrome P450' enzyme system. As a result, the levels of these drugs may be altered in the blood, and may cause a decrease in efficacy or potentially serious adverse reactions. Anyone using any other medications (for example 5-HTP, warfarin, carbamazepine, phenobarbital, HIV medicine, digoxin, oral contraceptives, SSRI's, Lithium, epilepsy medicine etc.) should check with their healthcare provider about possible interactions before taking this medicine. This medicine may also increase the risk of photosensitivity. Use cautiously in people with sensitive skin or those taking photosensitizing drugs. **Compliant to Guidelines**	Warfarin, ciclosporin, digoxin, theophylline and anti-convulsants. HIV protease inhibitors and HIV non-nucleoside reverse transcriptase inhibitors. Oral contraceptives, Triptans and SSRI. **Compliant to Guidelines**
Pregnancy and Lactation (MCC Guideline 2.16 Package Inserts for Human use, 2013)	If you are pregnant or breastfeeding, please consult your doctor, pharmacist or other healthcare provider for advise before taking this medicine. **Compliant to Guidelines**	Should not be used during pregnancy and lactation. **Compliant to Guidelines**
Dosage and Directions for use (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Take one capsule twice a day with meals, or as directed by your healthcare provider. **Compliant to Guidelines**	Take one to two capsules twice daily. Should the condition not improve within 4 weeks, please consult your practitioner. **Compliant to Guidelines**

PI Heading	Wellvita St John's wort Package Insert	Flora Force St John's Wort Package Insert
Side Effects (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Side effects may include gastrointestinal symptoms, dizziness, headache, confusion, mania, increased urinary frequency, allergic reactions, fatigue, photosensitivity, trouble sleeping and dry mouth. Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, discontinue use immediately and consult your doctor, pharmacist or other healthcare provider for advice. **Compliant to Guidelines**	Photosensitivity and gastro-intestinal symptoms. **Compliant to Guidelines**
Known Symptoms of Overdose and Particulars of Treatment (MCC Guideline 2.16 Package Inserts for Human use, 2013)	No known symptoms of overdose. Treatment is symptomatic and supportive. **Compliant to Guidelines**	Gastro-intestinal discomfort. Treatment is symptomatic and supportive. **Compliant to Guidelines**
Identification (MCC Guideline 2.16 Package Inserts for Human use, 2013)	White capsule. **Compliant to Guidelines**	Clear size 0 vegetable capsule containing brown to dark brown herbal powder. **Compliant to Guidelines**
Presentation (MCC Guideline 2.16 Package Inserts for Human use, 2013)	60 Capsules are packed in a plastic container. **Compliant to Guidelines**	60 Capsules packed into 125ml amber glass bottle with light green screw cap and safety seal insert **Compliant to Guidelines**
Storage instructions (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Store all medicines out of reach of children. Store in a cool dry place below 25˚C and keep away from direct sunlight. Keep the container tightly closed. **Compliant to Guidelines** **NAPPI CODE** 721451001 **(Nappi code inclusion in not required)**	Store below 25 °C. KEEP OUT OF REACH OF CHILDREN. **Compliant to Guidelines**
Registration Number	To be allocated. **Compliant to Guidelines**	To be allocated **Compliant to Guidelines**

(MCC Guideline 2.16 Package Inserts for Human use, 2013)		
Name and Business Address of the Holder of the Certificate of Registration (MCC Guideline 2.16 Package Inserts for Human use, 2013)	Alveta Healthcare (Pty) Ltd, 18 Greenwich Grove, Station Road, Rondebosch, 7700. Company registration number: 2004/021899/07. Pharmacy audit number: Y53008. **Compliant to Guidelines** **(Pharmacy Council Registration number not required)**	Flora Force Health Products (Pty) Ltd. P.O. Box 426, Rondebosch, Cape Town, 7701 **Compliant to Guidelines**
Date of Publication of the Package Insert (MCC Guideline 2.16 Package Inserts for Human use, 2013)	30 September 2013 **Compliant to Guidelines**	17/06/2015 **Compliant to Guidelines**
	This medicine has not been evaluated by the Medicines Control Council. This medicine is not intended to diagnose, treat, cure or prevent any disease. **Compliant to Guidelines**	

The Wellvita St John's wort has included additional information, not required for the Package Insert (PI). This could be because the company does not have a thorough understanding of the requirements of the SAHPRA according to the Guidelines, or it could also be used to communicate commercial information, e.g., NAPPI codes, to the pharmacist.

The Flora Force St John's wort PI has much less information in the Package Insert (PI) compared to the Wellvita St John's wort Package Insert (PI). The Wellvita St John's wort Package Insert (PI) contains 671 words, whereas the Flora Force St John's wort Package Insert (PI) is a third of the length with only 272 words. Wellvita St John's wort provides significantly more information in the following sections: "Contra-indications", "Warnings and Special Precautions", "Side Effects" and "Interactions". Where the Wellvita St John's wort PI has provided details in these sections, Flora Force St John's wort has merely provided one or two lines in each section. These sections relate to the safety of the product, so the difference is profound.

Neither Wellvita St John's wort nor Flora Force St John's wort have included the inactive ingredients of the capsule in the section on Composition. Flora Force St John's wort has listed a C0 scheduling status. There has been no addition in the List of Schedules (Regulations to Act 101 of 1965) that allow for a C0 scheduling status. It appears that some complementary manufacturers listed their products has a C0 in an attempt to comply with the call-up notice to register their products, but without an understanding of the scheduling status of medicinal products. A scheduling status is approved, on application to the SAHPRA, by the Naming and Scheduling Committee (MCC Guideline 2.36, 2014). A Schedule 0 medicine is one that is subject to registration, but does not appear in the List of Schedules (Regulations to Act 101 of 1965). Flora Force St John's wort has also not included the mandatory disclaimer that this product is not a medicine and not been evaluated by the SAHPRA. The statement appears on the label of the bottle, but the statement must appear in the Package Insert, as required by the Regulations to Act 101 of 1965.

Both Wellvita St John's wort and Flora Force St John's wort are compliant in the section on Interactions in that both PIs have listed interactions, but the two PIs provide very different information. Wellvita St John's wort attempts to explain the effects of St John's wort on the

liver and provides a short overview of classes of medicines that may be affected when taken in conjunction with St John's wort. The Flora Force St John's wort insert has simply listed the classes of drugs that interact with St John's wort without any explanation as to why they interact. The Wellvita St John's wort PI has not cross referenced the section on Interactions with other sections, such as Warnings, and have not listed the medicines known to interact by name or provided examples. Neither insert has adequately covered the safety of the product but has provided just enough information to protect themselves from legal action.

3.2.1 Critical Discourse Analysis

3.2.1.1 Critical discourse analysis of Wellvita St John's wort PI

Composition:
Each capsule contains: Active ingredients: St. John's Wort powder *(Hypericum perforatum)* 300 mg and St. John's Wort extract (*Hypericum perforatum*) [hypericin 0,3 %] 175 mg.

*Capsules are free of gluten, preservatives, sugar and lactose.

The Latin names for St John's wort is used in the composition of the product. The parenthesis and the italic lettering required of the Latin names distracts the reader from finishing the rest of the sentence. One might even miss that the capsules contain even more St John's wort than the 300 mg of the powder that is read first. The quantity of St John's extract is found only after the repetition of St John's wort, and more italics in parenthesis. Many people would not see the extra 175 mg in the capsule which makes the total daily dose per capsule 475 mg. The true composition, or what the product actually contains is not clear. We do not know what component of the St John's wort powder is active, where the powder comes from, and whether it is a standardized extract or not.

Indications
This product is used to relieve a slightly low mood and mild anxiety. This is based on traditional use only.

Wellvita St John's wort does not use the term 'depression' in their indications. They are not claiming efficacy for this indication, which is in line with the requirements for complementary medicines, and have moderated their claims, stating that their product is for a 'low mood and mild anxiety'. These are subjective terms, and not in line with the current DSM-5 definitions

of anxiety. The terms have been used colloquially to align with the commonly used expressions, and appeal to the lay-man.

The fact that the PI states that this indication is based on traditional use only informs the patient there is no clinical data, and the traditional use of the product through the ages has led to the indications of the product today.

Contra-indications
Do not use this use in medicine if you are hypersensitive (allergic) to any of the ingredients in the formula; or if you are pregnant or breastfeeding. Not suitable for use in children under the age of 18 years, or for longer than one year continuously, unless under medical supervision. Avoid use in patients with Alzheimers disease or any mental illness.

The contra-indications section is straightforward and simple. The medical term, hypersensitive, has been explained.

It is not clear from the wording on the insert whether the product is contra-indicated in children under 18, or whether it is only contraindicated if they use the product for longer than 1 year, or if no one should use the product for longer than 1 year without supervision from their healthcare professional. This product is available for purchase without medical supervision, yet the PI directs the patient to their doctor, pharmacist or other healthcare professional for supervision. This is contrary to what has been described in the PI as the product is available without a prescription or medical intervention and contradicts the text within the Package Insert (PI) which states that this product is natural and the implications that it is safe.

Mental illness is a is broad term and may refer to numerous conditions. People with low mood and anxiety as described in the indication, may have depression, and therefore a mental illness. Mental illness encompasses a huge spectrum of disorders, e.g. Autism, ADHD, Bipolar Disorders, even neurological conditions (Merriam- Webster, 2003). Caution is preferred to shameless marketing when it comes to medicines, however terms that may cause confusion, like mental illness, should be clarified.

Warnings and Special Precautions
If you suffer from any serious ailments or conditions; or if you are taking any prescribed medication, please check with your healthcare provider before taking this medicine.

• This medicine might slow blood clotting and should be used cautiously with any other blood thinning medication. Discontinue use two weeks prior to any scheduled surgery.

• Use cautiously if you have sensitive skin as this medicine might cause photosensitivity. Sunblock should be applied while taking this medicine.

• Do not suddenly stop taking this medicine, the dosage should be decreased over a period of time. Please consult your healthcare provider for further advice.

• This medicine can cause dizziness and can influence your ability to drive and use machines. Please exercise care when driving or operating machinery until you know how it affects you.

• Porphyria: Safety has not been established.

Nutritional supplements should not replace a balanced diet. Do not exceed the recommended dose without consulting a healthcare provider.

Wellvita St John's wort cautions the patient to consult their healthcare provider before using their product if they suffer from any serious ailment or condition. The definition of what a serious ailment or condition is, is left to the patient to decide.

Wellvita St John's wort provides a more comprehensive list of warnings before taking St John's wort than the Flora Force St John's wort product. While the tone of the insert is formal, the language used is not particularly medical, and the insert recommends the patient speak to a doctor before taking this product three times in this section alone.

The PI calls this product a nutritional supplement at the end of the section. Nutritional supplements do not carry the weight of a medicine, nor a complementary/alternative medicine. The phrase implies that there is a daily allowance of St John's wort to be taken. Nutritional supplements are taken to support the body's natural processes but are not generally used as a treatment. This reference makes the product seem very mild. Combined with other phrases and references to mild disease, this does not inspire confidence that this product will be effective and allows the patient to determine what is and is not serious, and what their approach to taking this medicine will be. By referring to itself as a nutritional supplement, it adds to the discourse about what is natural, and how natural is safe and mild, with gentle effects on the body. The term 'nutritional supplement' allows the patient to link

this medicine to vitamins and food stuffs in their mind, downplaying the medicinal aspect of this product.

The insert refers the patient to the doctor and calls itself a nutritional supplement in one section. This creates a disconnect as to what this product really is – a medicine with side effects and a clinical outcome, or a nutritional supplement supposed to support the body's natural processes. This gives the patient the agency to decide what this product should be.

Interactions
If you are taking other medicines regularly, including complementary or traditional medicines, or start taking any additional medicines while taking this medicine, consult your healthcare provider for advice. This medicine may interfere with the way the body processes certain drugs using the liver's 'cytochrome P450' enzyme system. As a result, the levels of these drugs may be altered in the blood, and may cause a decrease in efficacy or potentially serious adverse reactions. Anyone using any other medications (for example 5-HTP, warfarin, carbamazepine, phenobarbital, HIV medicine, digoxin, oral contraceptives, SSRI's, Lithium, epilepsy medicine etc.) should check with their healthcare provider about possible interactions before taking this medicine. This medicine may also increase the risk of photosensitivity. Use cautiously in people with sensitive skin or those taking photosensitizing drugs.

The PI provides a section on Interactions, however because of the use of complex medical and pharmacological terms and abbreviations the patient is likely not to read or understand the section as they do not understand the subject matter. A layperson will not know what the importance of the "liver's 'cytochrome P450' enzyme system" is and will probably skip this section. This section, compared to the rest of the PI, contains more medical terminology and is less likely to be understood by a patient with no knowledge of medical discourse.

The important information about which medicines interact with St John's wort is included in parenthesis and infers that this information is not important enough to get its own sentence, so the patient may be less likely to read it. The medical term "SSRI" denotes a whole class of anti-depressants called Selective Serotonin Reuptake Inhibitors and are a popularly prescribed anti-depressant. Most patients will not know the abbreviation SSRI, nor would they be reasonably expected to know how their anti-depressant medicine works. Mixing any of the SSRI or any other anti-depressant class affecting serotonin levels in the brain with St John's wort can result in serious side effects. The authors have only included the abbreviation, and not given even one example of a drug in this class. The inclusion of the

abbreviation “etc” at the end of the list of classes of medicines interacting with St John’s wort diminishes the importance of the interactions, and raises the question, of what is omitted by the inclusion of “etc”? Et cetera is often used in colloquial language to further a point already made and assumes the portion of the sentence referred to by “etc” is obvious to the reader or listener. In this case it is dangerous to assume the patient will understand what is meant by “etc”, when it is doubtful that they could understand the list. The classes of medicine listed as interactions varies greatly, and even for a healthcare professional, it will be difficult to discern what is meant by “etc”.

Photosensitivity has been mentioned three times in this insert, with no mention of what photosensitivity is, or what medications may cause it. The healthcare provider is mentioned numerous times throughout the insert. While this may present caution, it may also be shifting the responsibility away from the company, and onto the patient. The onus is again on the patient to seek help, as no prescription or interaction with a healthcare professional is required to purchase this product. This section calls the product a medicine numerous times, whereas in the previous section it referred to itself as a nutritional supplement. There is a lack of decisiveness from the manufacturers as to what this product is: Medicine or Supplement?

Dosage and Directions for use
Take one capsule twice a day with meals, or as directed by your healthcare provider.

Flora Force St John’s wort advises the patient they can take their dose as a single dose once daily, whereas the Wellvita St John’s wort product advises the patient to take the capsules with meals, twice daily. The reference to the health care provider as the product is not prescribed by the healthcare provider.

The dosing instructions are written simply, with the advice to speak to their healthcare professional. Again, the onus is on the patient to speak to their doctor.

Side Effects
Side effects may include gastrointestinal symptoms, dizziness, headache, confusion, mania, increased urinary frequency, allergic reactions, fatigue, photosensitivity, trouble sleeping and dry mouth. Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, discontinue use immediately and consult your doctor, pharmacist or other healthcare provider for advice.

The side effects section contains some intimidating adverse events. Once again, the medical terminology has been used excessively. Side effects like mania, gastrointestinal disturbances, and increased urinary frequency are vague and cover a host of different effects yet could be alarming to a patient who does not know what to expect from this product. One would need an understanding of medical terminology to understand these effects. These symptoms are also not congruent with the references to this product being mild and for a mild indication. The resulting tension means the patient must decide which stance to take on the product: mild and natural, or effective and medicinal, with a host of side effects and interactions.

3.2.1.2 Critical discourse analysis of Flora Force St John's wort

The Flora Force St John's wort PI is very short, and only a PI is presented in the product packaging. It does not have any of the recommended texts for patients, and only complies with the required heading for a PI.

Proprietary name (and dosage form): Flora Force St John's wort Capsules 300 mg
Composition: Each capsule contains Hypericum perforatum powder 300 mg.
Pharmacological classification: Category D Western Herbal Medicine
Pharmacological action: 1.2 Central nervous system Stimulants, psycho-analeptics (antidepressants)

The four headings that appear first on the PI are required by the SAHPRA 's Guidelines on PIs. These headings provide regulatory information regarding the strength, composition and pharmacological classification. A healthcare professional can interpret the information under each heading appropriately. However, a patient, having purchased this product off the shelf with no assistance from a healthcare professional, will not have the necessary tools to correctly interpret these headings.

The name of the product range “Flora Force” informs the patient of the natural origins of the product, and that it is still a potent remedy. The patient reads that the product is a Western Herbal Medicine, differentiating it from other disciplines of herbal medicines, such as Chinese Herbal Medicine, Ayurvedic Medicine and African Traditional Medicine. The term “western herbal” differentiates the various treatment theories in alternative medicine practices. However, by placing the words “Western Herbal Medicine” together as has been done in this case, reinforces the natural origins of the product, and refers to the product as a medicine. The term “medicine” implies there is scientific research and proof behind the claim. This was not done in the Wellvita St John’s wort PI, where the discipline was simply referred to as: “Discipline: Western herbal”.

Directly beneath that, the Pharmacological action calls the product a Central Nervous System (CNS) stimulant and an anti-depressant. This is incongruent with the idea of a ‘natural’ product. Natural products are assumed to be gentle on your system and not have the side effects associated with allopathic medicines, however the pharmacological action calls the product a CNS Stimulant and anti-depressant – products that are particularly potent and have a long list of side effects. The classification according to the list of schedules in the Regulations to Act 101 of 1965 is correct, however this is both incorrectly placed in the PI and perpetuates the claim that this product is an effective anti-depressant medicine. The wording under Pharmacological Action should have been included in the section above. The placement of these words in this section could be due to lack of understanding of the Guidelines, or to make the PI appear more professional. The use of words such a “psycho-analeptic” hold no value to a patient, other than to convey the idea that this product is as proven as an allopathic medicine, even though it is sold, and sells itself, as an herbal remedy.

Indications: Herbal medicine for the treatment of anxiety, nervous stress and mild depression.

The terms “herbal” and “medicine” are linked, and conveys the gentleness of nature, combined with the potency and effectiveness of medicine. The term “treatment” implies the product will be effective for anxiety, nervous stress and mild depression. Nervous stress and

mild depression are vague descriptors, and open to interpretation. The current medical definitions of anxiety and depression are not used in this PI. In this context, those words are used in a more 'traditional' sense, where depression and anxiety were synonyms for day-to-day or situational stress, rather than the medical conditions they are today. This PI does not give the patient any guidance as to what mild depression is, or when mild depression requires medical diagnosis. There is no guidance as to when treatment with St John's wort is appropriate, or when the treatment should be stopped or escalated to a doctor. As previously discussed, anxiety is now a recognised condition in the DSM-5, and generalised anxiety is one of the most common diagnoses in medicine (Kupfer D., 2015).

Contra-indications: Do not use with MOA inhibiting, or SSRI drugs and oral contraceptives, theophylline, simvastatin, and anti-histamine. Do not use when pregnant or breastfeeding.

The Package Insert (PI) misspelled the acronym for monoamine oxidase inhibitors (MAO inhibitors). This could be a finger error that was missed, or the person writing the insert was not aware of what the acronym meant.

Very few patients will understand this extremely important section. Most patients will not know what MAO inhibitors are, nor SSRIs. Monoamine Oxidase inhibitors are old products, and very rarely prescribed. This section compared to the Wellvita St John's wort insert is quite different. The Wellvita St John's wort insert has included conditions that are contra-indicated with the concomitant use of St John's wort, however, this insert only lists classes of medicines, and the active ingredient: simvastatin and theophylline. It also raises the question of only simvastatin, and not any other statin molecule was included.

The interactions listed in this section are also fundamentally different to each other. St John's wort may enhance the effect of an SSRI medicine through it's mechanism of action until toxicity occurs but will reduce the efficacy of the oral contraceptive by enhancing the metabolism of the hormones (Borelli and Izzo, 2009). The interactions in this section need to be explained more clearly. The European Union Herbal Monograph for *Hypericum perforatum L.* (2017) requires information regarding the types of interactions possible for St

John's wort, as it is a potent inducer of cytochrome P450 subtypes as well as p-glycoprotein. By grouping MAO inhibitors, SSRIs, and oral contraceptives together, the PI implies that they are all similar molecules, with similar mechanisms of action and potential interaction. A lay-person with no medical knowledge will not be able to correctly interpret or understand this section.

By only including the active names and therapeutic classes of medicines, the PI raises the question of how aware patients are of their various medicines and assumes that patients will know the active names and class names of their medications. Where these products are available to purchase without assistance from a healthcare professional the safety instructions need to be clear and easy to understand. Without explanation or clarification of the interactions, the reader is likely to disregard this section as they do not understand it, and the patient remains unaware of the safety aspects of this product.

Warnings: Discontinue use 3 days before any general anaesthetic and surgery.
Photo-sensitivity, avoid any exposure to ultra-violet lights and full sun.
Persons on SSRI drugs should not take St John's wort (*Hypericum perforatum*). Discuss with medical practitioner.

Use before general anaesthesia and surgery is foregrounded, so the patient will remember this section as being important, however, there is no guidance as to what may happen or why this product must be stopped before surgery, and there is no instruction to inform the healthcare professional that the patient is taking St John's wort before emergency surgery.

Medical terminology is used again with the term "SSRI drugs" and no explanation as to what they are or examples of common SSRIs a patient may know. There is no indication of the seriousness of the reaction that may occur when St John's wort is used with SSRIs.

Drug interactions: Warfarin, ciclosporin, digoxin, theophylline and anti-convulsants. HIV protease inhibitors and HIV non-nucleoside reverse transcriptase inhibitors. Oral contraceptives, Triptans and SSRI.

Only medical terms and drug names have been used in this section. Once again, the patient is expected to be aware of the active ingredients in their medicines, and to evaluate this PI for suitability and safety to their situation. No mention is made of what may occur should St John's wort be taken with any of the above-mentioned products, and by combining all these terms, it is implied that they have the same interaction. Oral contraceptives are mentioned again, however no mention of any other kind of contraception has been included indicating whether it is safe or not.

Pregnancy and lactation: Should not be used during pregnancy and lactation.

Selective Serotonin Reuptake Inhibitors such as fluoxetine are considered safe in pregnancy, however there is no research as to whether St John's wort is also safe. Other sections have been more direct with contra-indications, using words like "do not take with...", whereas this section, using a word like "should" implies that this is an option during pregnancy.

Dosage and directions for use: Take one to two capsules twice daily. Should the condition not improve within 4 weeks, please consult your practitioner.

There is no clarity on when it is appropriate to take 1 capsule or when to take 2 capsules. The term "condition" is vague, as the indications listed three possible conditions. There are varying degrees of anxiety. Nervous tension and the term 'mild depression' are very subjective. The terms "depression" and "anxiety" are misused in this context, as they are not compliant with the DSM-5, however they have been used in colloquial terms that the lay person is more likely to understand and relate to. The patient is left to decide how severe their 'condition' is and medicate accordingly. There is no instruction on stopping the product, or when to expect to feel a difference, or what to do if the patient experiences an adverse event.

Side-effects and special precautions: Photosensitivity and gastro-intestinal symptoms.

Photosensitivity is a medical term, and also very vague. There are degrees of photosensitivity associated with varying degrees of discomfort for various patients. Patients should be made

to understand that this product may increase sun sensitivity and cause burning more easily than normal and to take protective measures.
"Gastro-intestinal symptoms" are also very vague. These can include nausea, heartburn, pain, diarrhoea and a host of other symptoms. This vague description of gastro-intestinal effects may result in someone discontinuing therapy due to an unrelated incident, thinking it was caused by the St John's wort. The vague description of the symptom also raises questions for patients suffering with gastro-intestinal disorders, and whether the product would exacerbate the conditions. More questions than answers are generated by this section.

The Wellvita St John's wort package lists 11 different side effects, compared to the two side effects listed here. The European Union Herbal Monograph for *Hypericum perforatum L.* (2017) lists restlessness, fatigue, gastro-intestinal disturbances and photosensitivity as side effects that need to be included on the PI. The brevity of Flora Force St John's wort PI on Side Effects is significant compared to the Wellvita St John's wort PI. For a product available to the public online and without the assistance of a healthcare professional the brevity of this section may be used to convince a patient that this product is natural and safe.

Known symptoms of over dosage and particulars of its treatment: Gastro-intestinal discomfort. Treatment is symptomatic and supportive.

Once again, gastro-intestinal discomfort is the only symptom of overdose and is particularly vague. Discomfort can range from mild reflux to severe pain. A patient has no way of evaluating whether they are suffering the symptoms of an overdose or simply a side effect, and if they should get help or wait for it to pass. There are no mentions of hypersensitivity reactions, particularly when taken in combination with other psychoactive medicines, and no mention of when to consult a doctor or visit their nearest emergency room.

At first glance, the Flora Force St John's wort Package Insert seems nonintimidating and easy to read. However, on closer inspection the PI is vague and inadequate and has not been written with the patient in mind. The average patient does not have the knowledge to properly interpret this insert with regard to the safety and use of the product. Information that has been included in the Wellvita St John's wort insert is missing in this PI. All written

information about a product can be considered marketing material, so the absence, or lack, of safety information in a product available over the counter to a patient can be considered purposeful and intended.

Chapter 4: DISCUSSION

4.1 Valerian Root

Both companies that own Biral® and Calmettes Nite are registered pharmaceutical companies that manufacture and sell allopathic medicines. These companies have robust regulatory teams who have experience with the SAHPRA and the requirements of registration. It could be possible that the reason that Calmettes Nite lacks a PIL and that the PI has not yet been updated to current guidelines was due to resource constraints. Both Biral® and Calmettes Nite contain a dry extract of Valerian Root at approximately the same dosage (100 mg vs 125 mg). Calmettes Nite provides the extraction ratios, as well as the equivalent dose in the raw root, which Biral® does not do, so one knows how much Valerian Root is in each dose of Calmettes Nite, but not for Biral®. The patient or healthcare professional needs to trust that the manufacturing plant of the active ingredient is ethical and uses the same extraction method with every batch.

Both products say that they are used for anxiety or nervousness. Notably absent from the Biral® PI is the mention of Valerian Root as a sleep aid, especially because the mechanism of action was listed as a CNS depressant, and is classified as a tranquilizer. According to the Canadian Natural Health Product Monograph for *Valeriana officinalis* (2008), and the Merck Manual (Marko, M. G. and Der Mardersian A., 2017) Valerian Root is used as a sleep aid/promote sleep and relieve nervousness.

The most apparent difference between the two inserts is the pharmacodynamic and pharmacokinetics sections. Biral® provides minimal information, whereas Calmettes Nite provides clinical data to support their indications. The information presented in the Calmettes Nite PI comes from a study by Donath *et al* (2000). They showed a significant difference between Valerian Root and placebo on the effect of slow wave sleep latency in their double blind, randomised, placebo-controlled cross over study on 16 patients with previously established psychophysiological insomnia. A dose of 600 mg of the extract of Valerian Root was administered at bedtime for 2 weeks. Subjective parameters such as sleep quality, morning feeling, day-time functioning, and sleep period were assessed by means of a patient questionnaire. They concluded that Valerian Root had a positive impact on the sleep structure after multiple doses of Valerian Root and recommended it be used in the treatment

of insomnia in patient with mild psychophysiological insomnia. They also commented on the lack of adverse effects experienced with Valerian Root. These results put the use of Valerian Root in a positive light, however a small study of only 16 people is not a statistically relevant trial.

Neither PI discusses the pharmacology or pharmacokinetics of Valerian Root, even though studies have shown Valerenic Acid, the apparent active constituent of Valerian Root (Becker *et al*, 2014) potentiates $GABA_A$ receptors, contributing to Valerian Roots anxiolytic and sedative properties (Khoma *et al*, 2007; Becker *et al*, 2014). It was further demonstrated the potentiating effect of Valerian Root may be due to the inhibition of the breakdown of GABA in the brain (Bent *et al*,2006; Fernandez-San-Martin *et al,* 2010). A pharmacokinetic study in elderly women found considerable inter- and intra- variability of pharmacokinetic parameters and suggested that this may be the reason for valerian's inconsistency as a sleep aid (Anderson *et al*,2010). Further, the peak serum concentration of Valerian Root (Cmax) and the area under the curve (AUC) decreased, and half-life increased with an increased body weight (Anderson *et al*,2010).

A pooled patient population of 1093 patients examining the effects of Valerian Root on sleep showed a statistically significant increase in improved sleep in the valerian treatment groups, although the dichotomous and biased nature of the studies was cited (Bent *et al*, 2006). These findings were later echoed by a meta-analysis of 18 randomized placebo-controlled trials, where despite the heterogeneity of the data, the qualitative results suggested valerian was effective (Fernandez-San-Martin *et al*, 2010).

Conversely, Taibi *et al* (2007) concluded that while Valerian was a safe substance, it was not effective as a sleep aid. A Cochrane review evaluating the efficacy of valerian in treating anxiety found only one study involving 36 patients, and found that there was no difference between diazepam, Valerian Root or placebo for clinician-rated anxiety. They concluded more studies with more patients was required (Miyasaka, Atallah & Soares, 2006). Nunes and Sousa (2011) conducted a review of the evidence in literature of the efficacy of valerian on anxiety and sleep disorders and found no evidence to suggest efficacy of valerian in anxiety, and conflicting evidence of valerian's efficacy in treating sleep disorders. After a review of

available clinical trials, Saeed, Bloch and Antonacci (2007) recommended physicians do not use valerian for the treatment of anxiety due to a lack of robust evidence.

Neither PI lists any known interactions, even though Valerian Root may inhibit CYP3A4 metabolism, and p-glycoprotein activity as shown through in-vitro studies (Marko, M. G. and Der Mardersian A., 2017). However, there are no clinical studies showing any interactions through drug metabolism (Marko, M. G. and Der Mardersian A., 2017).

The doses of Valerian Root used for insomnia vary between 225 mg to 12 g (Bent *et al*, 2006; Canadian Natural Health Product Monograph for *Valeriana officinalis*, 2008; Fernandez-San-Martin *et al*, 2010; Marko, M. G. and Der Mardersian A., 2017). Biral® recommends 200 mg taken at eight hourly intervals, and the Calmettes Nite package insert recommends up to 3750 mg of the root can be taken as a single oral dose at night and therefore falls into recommended range for all standardised extracts for Valerian Root. No statement on duration of use is required as per the Canadian Natural Health Product Monograph for *Valeriana officinalis* (2008).

A small study conducted by Anderson *et al* (2005) found the peak plasma concentrations after a 600 mg oral dose of Valerian Root showed peak plasma levels between 1 and 2 hours after dosing, which correlates to the recommendation to take the dose 30 minutes to 2 hours before retiring to bed.

Calmettes Nite does not recommend use of their product in children younger than 12. A study published in 2016 examined the use of Valerian Root, St John's Wort and passionflower on 115 children aged between 6 and 12, suffering from nervousness and agitation, including agitated depression (Trompetter, Krick and Weiss, 2013). The authors found that the combination including Valerian Root was well tolerated (97.4%), with only mild side effects reported. Gromball *et al* (2014) administered Valerian Root and lemon balm to children under the age of 12, suffering from hyperactivity and concentration difficulties and found it to be safe and effective, with only 2 out of 169 children experiencing mild side effects.

A study of 102 volunteers found there was no difference in alertness, reaction time, or concentration when compared to placebo, versus the effects of flunitrazepam, even after 14 days of treatment (Kuhlman *et al*,1999). The side effects mentioned by the Canadian Herbal monograph for Valerian Root (2008) were that some people may experience drowsiness. Caution must be exercised if operating heavy machinery, driving a motor vehicle or involved in activities requiring mental alertness within 2 hours of consumption. Valerian Root may prolong the effect of other sedatives and may affect driving or other activities requiring alertness (Merk Manual, Online Edition, 2017). Only Calmettes Nite carries this warning in the section on Side Effects.

In a pooled patient population of 1093 patients, only one of the trials identified diarrhoea as an adverse event, but the trials included did not have a defined way of reporting and collecting information on adverse events (Bent *et al*, 2006). Bent *et al* (2006) also found that the patients receiving Valerian Root had the same incidence of hangover as the placebo, and less than that of benzodiazepines. Taibi *et al* (2007) concluded that valerian was a safe and only associated with rare, mild adverse events, as did Nunes and Sousa (2011). A review of placebo-controlled clinical trials also found the incidence of diarrhoea was much higher in the patient populations receiving valerian (Fernandez-San-Martin *et al* 2010). Other side effects included pain in the upper abdomen, nausea and heartburn as gastrointestinal side effects, and headaches, nervousness and drowsiness as the central nervous system side effects, however these were all mild and there was no difference when compared to placebo (Fernandez-San-Martin *et al*,2010). Neither of the examined PIs list the possibility of diarrhoea as a side effect, with Calmettes Nite only alluding to mild gastrointestinal disturbances in the event of an overdose.

The Calmettes Nite PI gives more information on potential effects of an overdose than Biral® PI, however they both agree that there are no toxic effects in the event of an overdose. A case report of a valerian overdose in which the patient took 20 times the recommend dose of valerian, presented with mild symptoms, all of which resolved within 24 hours (Willey *et al*, 1995).

The heterogeneity of the studies available for Valerian Root means there is no clear conclusion to be drawn from the literature about the root's efficacy in sleep and anxiety. The pooled patient population of 1093 patients consisted of 16 clinical studies, most of which had methodological problems, yet found the product improved sleep when the sleep quality measure was pooled (Bent *et al*, 2006). A systematic review of the literature presented 36 articles that matched the criteria for the study, 8 of which were open label studies, the rest were controlled for safety and efficacy (Taibi *et al*, 2007). A Cochrane review found only 1 study out of 36 to fit their evaluation criteria (Miyasaka, Atallah & Soares, 2006).

Critical discourse analysis of Valerian Root inserts

Both Biral® and Calmettes Nite tablets emphasize the natural origins of the product, reinforcing the common notion that natural medicines are less harmful than allopathic medicines, as they are organic and natural, reinforced by statements such as "no known adverse effects". Biral® describes the active ingredients as "natural products of plant origin" and Calmettes Nite similarly, describes itself as a "herbal medicinal product". Even though both products reinforce their herbal, natural status, they employ a medical discourse to convey efficacy and importance, lest the patient think they might be ineffective. Sections in the PIL such as "What Biral® is used for" cements the idea of "natural" and "plant" in the patients' mind, while further along in the sentence some 'light' medical terminology is used: "central nervous system" and "mild sedative action".

The normal doses of Biral® and Calmettes Nite are not clearly explained to the patient, however these doses are constructed under Side Effects as a scientifically prescribed dose. In the Side Effects sections of the inserts, the language switches from one used for a lay person to a medical discourse and confuses the reader, discouraging them from reading further. It is no coincidence that this switch has occurs in the Side Effects section, which is the section where the dangers of the medicine are clearly described, and the only section of the PIL that may dissuade a consumer from purchasing the product. However, because many patients buy this product without the advice from a healthcare professional, the placement of the medical jargon in this section, uses medical discourse to potentially exclude the patient from knowing and understanding this section.

Within the section on tablet composition in the Calmettes Nite PI, the active ingredient is referred to as both Valerian dry root extract and extract of plant root *`Valeriana officinalis*'. In the section about pharmacodynamics properties, the active ingredient is referred to as Valerian Root extract, under pharmacokinetic properties it is referred to "extract of Valerian Root" and in contra-indications it is referred to as "root of Valerian". The inconsistent use of the term "Valerian Root" may be read as different substances with different strength. By writing the active ingredient in a long, more formal way, it makes the sentence a more scientific, medical text. The recommendation from the guideline on PILs (Guideline 2.14, 2013) is to use the name of the product, instead of the active ingredient, to reduce confusion and improve readability by the patient.

Although the Calmettes Nite insert is thick with medical jargon, it provides the discerning, educated reader more information on the safety profile of Valerian Root compared to the Biral® PIL. The Biral® PIL relies heavily on the wording from the guideline on PILs (Guideline 2.16, 2013) and the authors have not supplemented this with information relevant to the patient, e.g., the use of Biral® and alcohol, or in the presence of liver disease.

4.2 St John's wort

St John's wort has been studied extensively due to the numerous drug-drug/CAM-drug interactions. As a strong substrate for CYP3A4 isoforms, St John's wort affects the metabolism of many prescription medications yet remains the most popular complementary treatment for depression (Soleymani *et al* 2017).

Neither the Wellvita St John's wort, nor the Flora Force St John's wort Package Insert has listed the pharmacology, pharmacokinetic or pharmacodynamics of St John's wort. The anti-depressant activity of St John's wort has been ascribed to the chemical hyperforin and hypericin, the active component of St John's wort (Canadian Natural Health Product Monograph for *Hypericum perforatum*, 2009; Fasinu, Gurley and Walker, 2016; Fava *et al*, 2005). Hyperforin is thought to inhibit the uptake of GABA, dopamine, nor-adrenaline and serotonin, and works synergistically with other phytochemicals found in St John's wort to

alleviate depression (Fasinu, Gurley and Walker, 2016; Marko, M. G. and Der Mardersian A., 2017).

The United Kingdom, and other European and American Health Authorities, review data submitted in a dossier by the manufacturer of all medicines on the market, including registered complimentary medicines. They review all the submitted data with a focus on the quality, safety and efficacy of a product, and publish their decision as to whether or not to renew the product licence in a document called a Public Assessment Report (PAR). The PAR is made available to the company and the public, and lists the conditions for registration, as well as any limitations. The Wellvita St John's wort wording on indications is the same that published in the UK's regulatory authority's PAR (2011) for a registered St John's wort Capsules, which was granted a renewal of the registration.

The reported efficacy of St John's wort varies between researchers. In a multicentre, randomised, double blind, placebo-controlled trial it was found there was no difference between St John's wort and placebo (Shelton *et al*,2001). However, another randomised placebo-controlled trial (n=87) found no difference between 900 mg – 1800 mg St John's wort extract and 50 – 100 mg sertraline in major depression, leading the researchers to recommend St John's wort over sertraline due to the side effect profile of the herb (van Gurp *et al*,2002). A randomised, double blind placebo-controlled trial (n=324) compared treatment with 250 mg St John's wort extract to 75 mg imipramine in patients with mild to moderate depression and similarly, found there to be no difference in the Hamilton-Depression rating scale between the two treatments (Woelk, 2000). A Cochrane review (Linde, Berne and Kriston, 2008) found St John's wort effective in treating major depression, when compared to other anti-depressants, but also noted that the source of the St John's wort seemed to have an effect on efficacy, with the German sourced plant being more effective with fewer side effects.

Because of the powerful effects on the CYP isoforms in the liver, and the P-glycoprotein in the gut, St John's wort has several clinically significant pharmacokinetic interactions (Borelli & Izzo 2009). Both inserts advise the patient not to take St John's wort if they are allergic to

any of the ingredients under contra indications, however the Canadian monograph of St John's wort lists the following as contra-indications:

- anti-cancer medications,
- blood thinners,
- anti-depressant medications (e.g. selective serotonin reuptake inhibitors (SSRI)),
- anti-HIV agents,
- cardiovascular medications, immunosuppressants,
- contraceptive medications

Borelli and Izzo (2009) and the UK PAR (2011) describe interactions between St John's wort and anaesthetic agents, yet only the Flora Force St John's wort PI mentions stopping the product 3 days before general anaesthetic. The UK Public Assessment Report (2011) on Solgar's St John's Wort advises the patient on stopping treatment 10 days before surgery and cautions the patient on photosensitivity reactions, and consulting a doctor should symptoms worsen, or if they do not feel any different after 6 weeks under warnings and special precautions. The Wellvita St John's wort PI states that the product should not be used longer than 1 year, yet the Canadian Herbal Monograph for St John's wort (2009) recommends the treatment should not continue beyond 18 weeks.

Borelli and Izzo (2009) state that in isolation, St John's wort has an excellent safety profile. However, when taken in combination with other substrates of cytochrome P450 and P-glycoprotein, St John's wort causes very serious interactions. 147 known interactions between St John's wort and other medicines have been documented (Tsai *et al,* 2012). Well documented interactions include low blood levels of cyclosporine, serotonin syndrome when co-administered with other SSRIs, failure of hormonal contraceptives, and reduced plasma concentrations of antiretrovirals and antiplasma medicines, warfarin, antihyperlipidemic agents, calcium channel blockers, beta-adrenergic agents, antianginal medicines, inotropic medicines, HIV drugs, chemotherapeutic agents, benzodiazepines, anti-depressants, antiepileptics, methadone, anaesthetic agents and centrally acting muscle relaxants, anti-histamines, theophylline, antidiabetic medicines, PPIs, antibiotics and antifungals (Borelli & Izzo 2009, UK PAR 2011).

The UK Public Assessment report (2011) of Solgar's St John's wort details the pharmacodynamics and pharmacokinetic interactions of St John's wort due to the influence of CYP 450 and P-glycoprotein and provides a full list of the possible medicine-CAM interactions that occur with St John's wort. Neither Wellvita St John's wort nor Flora Force St John's wort have included any pharmacodynamics nor pharmacokinetic information on their PIs, even though the information is available.

Both products have similar dosage recommendations. However, two capsules of Flora Force St John's wort provide one with 600 mg St John's wort powder, whereas the Wellvita St John's wort dose is 950 mg per two capsules. The UK Public Assessment Report granted a Traditional medicine licence to Solgar's St John's Wort based on 600 mg per dose.

The compounds identified as the active ingredients in St John's wort are hypericin and hyperforin (Natural Health Product Monograph: St. John's wort. *Hypericum perforatum* – Oral, 2009). The Canadian herbal monograph also specifies the dosage according to the percentage hypericin (0.12 -0.28) and hyperforin (3-6%). The Merck Manual recommends doses of 300 mg to 900 mg once daily of standardized preparation to 0.2-0.3 % hypericin and 1-4 % hyperforin (Marko, M. G. and Der Mardersian A., 2017). There is very little information as to whether both compounds are required to have an effect, or what effect could be expected with only one or the other. The fact that the percentage required by the Merck Manual and Canadian Monograph are so low, it is clear these compounds are extremely potent, yet there is no measure of the potency of the individual compounds. There is also no indication as to whether these compounds contribute to the development of Side Effects. Flora Force St John's wort does not list what kind of extract was used, nor do they provide the percentage of hypericin or hyperforin in their extract. 175 mg of the Wellvita St John's wort capsule contains 0.3 % hypericin, as they have stated under composition, but the powder of St John's wort making up the other 300 mg of the dose in both the Flora Force St John's wort PI and the Wellvita St John's wort PI does not specify its purity, or whether it is a standardised extract, or what part of the plant has been powdered. Very little information on the composition and potency of the St John's wort products is provided, which makes it difficult to draw conclusive comparisons to the monograph.

Numerous studies have shown that St John's wort has a good safety profile when used in isolation and that St John's wort was well tolerated among patients, with minimal reported side effects and greater tolerability than anti-depressants (Woelk, 2000; Shelton *et al*,2001; van Gurp, 2002; Fava *et al,* 2005; Linde, Berner and Kriston, 2008 and Borelli & Izzo, 2009).

There is a very noticeable difference in the list of side effects between the two package inserts (PI) examined. The UK Public Assessment Report on Solgar's St John's Wort (2011) approved a similar list of side effects to what the Wellvita St John's wort product has listed, while the Flora Force St John's wort PI has only listed 2 of the side effects. Data on Side Effects and interactions have been published and are freely available but has not been included in the inserts. St John's wort contains potent compounds which have an effect and side effects, but because there is a lack of regulatory oversight, CAM manufacturers treat the Guidelines as voluntary and only include the information which suits them. If this product were subject to the scrutiny required of allopathic medicines, the provided inserts would paint a very different picture.

Both PIs' contents could reasonably be verified in the literature. The UK PAR and Borelli and Izzo (2009) both list anaesthetic agents as medicines that interact with St John's wort, and only the Flora Force St John's wort PI mentions stopping St John's wort prior to elective surgery. Wellvita St John's wort mentions stopping their product prior to surgery but as a risk related to bleeding. Neither PI includes instructions to inform their doctors that they are taking St John's wort as a general precaution. Wellvita St John's wort advises no one younger than 18 should be on their product, and no mention of appropriate ages appear in the Flora Force St John's wort PI. Although there are some small studies available that demonstrate safety in children (Webber *et al*, 2008), there is not enough data to make this claim.

As seen with Valerian Root, the literature is inconsistent in its outcomes about St John's wort. A Cochrane review suggested that the St John's wort plants grown in Germany seemed to be better tolerated and more effective (Linde, Berne and Kriston, 2008), but there are no comparative studies available comparing the efficacy and side effect profile of plants grown in various regions.

The quality of the available published studies is poor, so it is difficult to get a holistic view of the action and safety of St John's wort. A clinical trial of the same standard as that expected from allopathic medicines is tremendously expensive. CAM manufacturers neither have the capital required for this study, nor the will to fund other studies. The results from these studies will probably show that St John's wort and its active compounds should be registered substances. Should this occur, St John's wort will lose its complementary status, and the right to make claims associated with complementary medicines. Scheduling the product and monitoring the claims of St John's will drastically reduce the market share the product currently enjoys.

Critical discourse analysis of St John's wort product inserts

Wellvita St John's wort has assigned an S0 scheduling to their product, however the registration number is yet to be confirmed. The Scheduling status of a product may only be assigned once the product has been evaluated by the Naming and Scheduling committee (MCC Guideline 2.36, 2014), so Wellvita St John's wort is either assuming a scheduling status or has included the status as a marketing tool to convince a patient that their product has been evaluated like a medicine. This is also in conflict with the rest of the package insert, where it refers to itself as a nutritional supplement.

The two St John's wort package inserts (PI) are quite different from each other, both in structure, content and compliance with the SAHPRA guidelines. The Wellvita St John's wort PI is more comprehensive and gives the patient a better idea of the risks of taking the product, whereas the Flora Force St John's wort PI has given the bare minimum information, to the point of excluding information from the PI. The Flora Force St John's wort PI was written using mostly medical terminology, unlikely to be understood by a patient. In particular, the sections about contra-indications, drug interactions and side effects were very heavy in medical terms. This over-reliance on medical terminology discourages a lay person from reading the section.

The section on Side Effects of the Wellvita St John's wort insert contains the most unexplained medical terminology between the examined PIs. There have been many references

throughout the PI to this product being mild, it is for a mild disease, and has referred to itself as a nutritional supplement. This section details that St John's wort has significant interactions and can have a significant impact on your health if used with certain other medicines. This section could potentially deter a cautious patient, looking for a mild solution. By writing this section in this way, the author is excluding the patient from this section, yet because the section is still in the insert, the company has protected itself.

Wellvita St John's wort provided more complete information than Flora Force St John's wort. Both products have similar lists of interactions, but the Wellvita St John's wort PI provides a better description of the warnings and special precautions. Because of the severity and numerous interactions with St John's wort, the listed interactions should be more comprehensive and in an easier to read and understand format for patients. Tsai *et al* (2012) and Linde, Berne and Kriston (2008) recommend more vigilance on the part of the practitioner, and a greater focus on the PI and PIL to provide both patient and practitioner information on the risks of taking St John's wort.

Chapter 5: Conclusions and recommendations

In line with the structure of this report, the valerian products will be discussed together, and the St John's wort products will be discussed together, and not compared to each other. The fact that these two products are so different, and yet should be compliant to the same guidelines and evaluated within the same therapeutic classification demonstrates how little cohesion there is from the regulator regarding Complementary and Alternative Medicines. Allopathic medicines are evaluated more methodically and rigorously, resulting in predictable formatting and information presentation. A conclusion and recommendation for each of these products follows.

5.1 Valerian Root

Biral® and Calmettes Nite are both manufactured by international pharmaceutical companies, with teams of regulatory affairs and drug safety specialists around the world. The PIs and PILs for these two products are written by pharmacists and regulatory professionals both abroad and locally. The result can be seen in the construction of the PI information and the level of compliance of the PIs to the Guidelines.

The studies showing the efficacy of valerian available are small and lack robust evidence, producing equivocal data. These complementary products are not well researched, with much of the data based on anecdotal studies, case reports and small clinical trials, resulting in the assumption that the products are safe and effective in treating every day conditions. The information and claims made in the Valerian Root inserts could be verified in the Canadian Monograph and Merck Manual, as well as with published studies. However, the validity of these studies used to generate the text has been overamplified. For example, the study used by Calmettes Nite to support the information under the pharmacodynamic properties only included 16 subjects (Donath *et al*, 2000*)*. The studies supporting the use of Valerian Root were small, with little statistical power to prove efficacy. Studies with pooled patient data such as Cochrane Reviews and meta-analysis of published trials found there to be insufficient evidence to support the use of Valerian Root and showed the flaws in the design and data collection of the smaller trials (Taibi *et al*, 2007; Miyasaka, Atallah & Soares, 2006; Saeed, Bloch & Antonacci, 2007; Bent *et al*, 2006; Fernandez-San-Martin *et al*, 2010).

The studies chosen for inclusion into the inserts were only those that showed the effectiveness and beneficial effects of the products. Information demonstrating the variability of the pharmacokinetic parameters in elderly women (Anderson *et al*, 2010) was not included in either the Biral PI or Calmettes Nite PI. Information is available on these sections which may influence the use of the product yet is not included in either of the examined inserts.

Despite the lack of evidence to support the claims of Valerian Root as a sedative and tranquilising agent, the majority of the studies reviewed, as well as the Canadian monograph and Merck Manual, conclude that although there is very little data showing the efficacy of Valerian Root, it is a safe substance with minimal side effects and is well tolerated by patients (Taibi *et al*, 2007; Canadian monograph for Valerian Root, 2008; Miyasaka, Atallah & Soares, 2006; Marko, M. G. and Der Mardersian A., 2017).

The language used in the construction of the Calmettes Nite PIs and Biral PILs available for the patient was contradictory and promotional. The language varies from simple and straightforward to complicated medical terms in certain sections. The sections in both the Biral PIL and the Calmettes Nite PI that were written more simply were: indications, pharmacological action and dosage. These sections emphasised the natural origins of the product, while the sections describing the risks of the product are written in medical terminology and contradict earlier assertions of safety and a lack of side effects. The use of medical terms in these sections discourages a non-medical patient from reading further and promotes the product as a safe and natural product in the mind of the consumer.

Complementary products are readily available to buy off the shelf in most pharmacies and from online stores, without any interaction with a healthcare professional required. The fact that so much medical terminology has been used in the inserts of these products is significant as the patient does not have the knowledge to read and understand the PIs and PILs of the respective products, nor understand the risks of taking these products. Words like ‘natural origin’ and ‘plant based’ portray the product as a natural remedy, whereas medical terms like ‘idiosyncrasies’ and ‘hypersensitivity’ are used to describe the side effects and contra-indications of both valerian products creates an inconsistent and contradictory text for the

patient to read. The inclusion of these medical terms only serves the needs of the manufacturer, as the company has complied with the legal requirements of advising the reader of the risks of the product but have worded the information in such a way that is inaccessible to many readers. In doing so, it appears as through the natural and safe aspect of the product is promoted over and above the safety of the product.

5.2 St John's wort

Unlike the Valerian Root inserts, the St John's wort products are not manufactured or sold by international pharmaceutical companies, and both products are available in health shops and online. Both St John's manufacturers advertise themselves as nutritional or nutritional supplement manufacturers.

While the information contained in both the Flora Force St John's wort PI and the Wellvita St John's wort PI could be validated in the literature, the manufacturers appeared to choose which information appeared in the inserts and which information was excluded. The Flora Force St John's wort PI was significantly shorter and contained less information than the Wellvita St John's wort PI. This discrepancy shows there is no over sight from the regulator, and there is very little effort from the industry to comply to the guidelines published by the regulator.

The literature review shows that the active components of St John's wort are very potent – hypericin should be present at a concentration between 0,12 % and 0,28 % (Canadian Monograph for St John's wort, 2009) or between 0.2 % and 0.3 % (Marko, M. G. and Der Mardersian A., 2017), and hyperforin should be between 3 % and 6 % (Canadian Monograph for St John's wort, 2009) or between 1 % and 4 % (Marko, M. G. and Der Mardersian A., 2017) depending on which monograph is being followed. Two head to head trials and a Cochrane review showed that St John's wort was effective for moderate to severe depression, compared to conventional allopathic medicine (van Gurp *et al*, 2002; Woelk, 2000; Linde, Berne and Kriston, 2008).

Both company PIs have omitted information regarding the pharmacodynamics and pharmacokinetics of the products, even though this information is freely available. The list of

interactions is incomplete and not written in a patient friendly way, particularly in the Flora Force St John's wort PI. Both the Wellvita St John's wort PI and the Flora Force St John's wort PI uses technical medical terminology and acronyms such as: 'SSRI's' and 'cytochrome P450' and 5-HTP. By including these risks in medical terms and abbreviations the manufacturers disguise the risks of the products. The risk of interactions and potentially severe side effects is high with a product like St John's wort that interacts so strongly with the cytochrome P450 system.

The words natural, mild, plant-based, and natural origin are used throughout the St John's wort inserts. The use of these words in the indications and description of the pharmacology of the product allow the patient to make their own links between the natural and safe status of the product. Both inserts use the terms in such a way so that the natural, mild status of the medicine is reinforced; this medicine will complement your body and the mild side effects make it safe to use. The link between natural and safe is played upon heavily and constantly reinforced in the patient's mind. The Wellvita St John's wort Package Insert refers to itself as a nutritional supplement in the section on warnings and special precautions, further downplaying the risks associated with taking this product, and reinforcing the natural and therefore safe status. The name "Flora Force" also alludes to the product range's link to nature, and reinforces this in the short package insert, under "Indication", where it describes itself as an herbal medicine.

There was a greater effort placed on including marketing terminology into the inserts than on educating the patient on the use and safety of the products. Wellvita St John's wort referred to itself as a nutritional supplement, and downplays the risk, side effects and even indications by continuously referring to itself as a mild product. The marketing language in the Flora Force St John's wort insert is subtler than that of Wellvita St John's wort, however the exclusion of important safety information, and the excessive use of medical terminology, and the brevity of the insert can be viewed as a way of downplaying the risks, and the negative associations of the medicinal aspects of the product.

The Wellvita St John's wort PI was mostly constructed in compliance with the guidelines by using the required text, yet the impact of the medicine, and the seriousness of what it does

is lost. This can result in patients not taking the medicine properly, and not understanding the implications of side effects and interactions. By comparison, none of the required texts appeared in the Flora Force St John's wort insert, and the overreliance of medical jargon makes the PI very difficult to read and understand for a non-medically educated patient.

None of the examined PIs or PILs conveyed the safety of the products to the reader in a meaningful way. The sections on side effects, interactions, contra-indications and warnings were inadequate or incomplete and confusing in all the package inserts (PI) examined.

5.3 Recommendations

The compliance of the PIs and PILs to the Guidelines published by the SAHPRA needs to be improved. This will only happen with greater oversight from the regulator, as well as a greater investment by the manufacturers in their staff resources and willingness to develop a balanced and fair Package Insert (PI). This willingness to develop fair and balanced product information to be included in the Package Insert falls to corporate responsibility to ensure their consumers have the correct and complete information available in a manner that is accessible and understandable. In order to ensure compliance with the guidelines and regulations, industry and the regulator must work together to protect the patient and promote proper use of the medicines. For example, St John's wort appears to have some efficacy in the treatment of depression, but there is a lack of oversight from the regulator with regards to the use of the medicine. The onus lies with both the regulator and the manufacturer to ensure the risks are clearly stated, and the product is used properly.

Both complementary products manufacturers and the regulator need to decide whether these products are medicines or nutritional supplements and state this clearly. Medicines have risks and side effects, and these need to be stated clearly and unambiguously, however many complementary medicines are portrayed as nutritional supplements. By sitting in between a safe and natural substance and a medicine, the patient is left to decide on the risks of the products, and the regulator has failed to provide a clear and unambiguous stance on the products. The resulting confusion allows the manufacturers to include unnecessary information in their Package Inserts (PI) and position their products in the way that suits their needs best.

Industry, particularly those in new areas of regulation such as complementary medicines, need to self-regulate. There needs to be a concerted effort in both regulatory compliance and a focus on patient safety, rather than simply including text to comply with regulation.

The results of this study can be used to assist the authors of the package insert to question and critically examine the way a package insert is written. This research can further assist the regulatory pharmacist writing the PIL so the language used is easily understandable, and unambiguous, and does not impair a reader from gaining the required information on the product to make an educated decision about the risks of taking the product.

Foucault's theory of power and discourse is that knowledge and power are inextricably linked and are often written in ways to control more than simply the production of meaning (Pinkus 1996). In light of this, one could say that medical discourse has become a dominant discourse within society, and those who understand it, hold a position of power.

The patient has a responsibility to understand the risk and benefits of what medicines they are taking, however, where a discourse has separated patients from healthcare professionals there need to be active collaboration between the industry, the pharmacists writing the PIs and PILs, and doctors, with an oversight from the regulatory bodies.

5.4 Limitations

It was not within the scope of this study to approach the companies marketing these products for reasons or insight into how these Package Inserts (PI) were populated, and what regulatory advice was received, and decisions taken in creating these Package Inserts (PI); nor to approach member of the public to gain insight into their understanding of the package insert. Future work can address these limitations.

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Appendix A – Biral® PI and PIL

Package Insert

Biral® sugar-coated tablets

SCHEDULING STATUS:
S0

PROPRIETARY NAME AND DOSAGE FORM:
Biral® sugar-coated tablets.

COMPOSITION:
Each tablet contains:

Valerianae extractum siccum	100,0 mg
Passiflorae extractum siccum	45,0 mg

Contains sugar

PHARMACOLOGICAL CLASSIFICATION:
A 2.6 Tranquillizers.

PHARMACOLOGICAL ACTION:
Valerian and Passiflora are natural products of plant origin, which act on the central nervous system to bring about a mild sedative action.

INDICATIONS:
Anxiety, restlessness and minor neuroses characterised by the absence of depression.

CONTRA-INDICATIONS:
Hypersensitivity to the ingredients.
There are no known contra-indications.

INTERACTIONS:
No known interactions.

PREGNANCY AND LACTATION:
Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:
Adults: Unless otherwise directed, initially two tablets should be taken with water three times daily after meals. After improvement or in less severe cases, one tablet should be taken three times daily after meals.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
Adverse reactions with normal therapeutic doses are unknown. Should any adverse reaction occur, discontinue medication immediately.
Hypersensitivity has been known to occur with the use of Passiflorae extractum siccum.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Overdose or prolonged use should not give rise to any toxic effects. However, should any severe symptoms occur following overdose, consult a medical practitioner or nearest hospital immediately.

IDENTIFICATION:
Pale pink sugar-coated tablets.

PRESENTATION:
Available in blister strips, packed in cartons of 20, 40 and 100 tablets.

STORAGE INSTRUCTIONS:
Store in a cool, dry place. Store at or below 25 °C.
Store out of reach of children.

REFERENCE NUMBER:
B1503 (Act 101/1965).

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
TAKEDA (PTY) LTD
1 Libertas Road
Cnr. Main Road & Sloane Street
Bryanston, 2191

DATE OF PUBLICATION OF THE PACKAGE INSERT:
09 December 2008

CC14/064

PATIENT INFORMATION LEAFLET

WHAT YOU NEED TO KNOW ABOUT Biral®
- Please read this leaflet carefully before you start using this medicine.
- Keep this leaflet with your medicine as you may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

SCHEDULING STATUS
S0

Biral® is a schedule 0 medicine which means it can be sold without a prescription.

PROPRIETARY NAME AND DOSAGE FORM
Biral® sugar-coated tablets.

WHAT Biral® CONTAINS
Each **Biral®** sugar-coated tablet contains:

Dry extract of Valerian	100,0 mg
Dry extract of Passion Flower (Passiflora)	45,0 mg

Other ingredients:
Lactose, croscarmellose sodium, polyvidone, magnesium stearate, microcrystalline cellulose, methylhydroxypropyl cellulose, silicon defoaming emulsion SE2-MC, sucrose, calcium carbonate, talc, colloidal silicon dioxide, acacia, titanium dioxide, iron oxide black, iron oxide yellow, iron oxide red, beeswax, carnauba wax.

WHAT Biral® IS USED FOR
Valerian and Passiflora are natural products of plant origin, which act on the central nervous system to bring about a mild sedative action.

BEFORE TAKING Biral®
Do not take this medicine if you are allergic to the ingredients.

If you are taking other medicines on a regular basis, the use of this medicine as well may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice.
If you are pregnant or breastfeeding a baby please consult your doctor, pharmacist or other health care professional for advice before taking this medicine.

HOW TO TAKE Biral®
Adults: Unless otherwise directed, initially two tablets should be taken with water three times daily after meals. After improvement or in less severe cases, one tablet should be taken three times daily after meals.

SIDE-EFFECTS
Adverse reactions with normal therapeutic doses are unknown. Should any adverse reactions occur discontinue medication immediately. Hypersensitivity has been known to occur with dry extract of Passion Flower (Passiflora).
Not all side-effects reported for this medicine are included in this leaflet. If your general state of health worsens while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.

STORAGE AND DISPOSAL INSTRUCTIONS
Store in a cool, dry place. Store at or below 25 °C.
Store all medicine out of reach of children.
Take unused or expired medicine to your doctor, pharmacist or other health care professional for safe disposal.

PRESENTATION
Available in blister strips, packed in cartons of 20, 40 and 100 tablets.

IDENTIFICATION
Pale pink sugar-coated tablets.

REFERENCE NUMBER
B1503 (Act 101/1965).

NAME AND ADDRESS OF REGISTRATION HOLDER
TAKEDA (PTY) LTD
1 Libertas Road
Cnr. Main Road & Sloane Street
Bryanston, 2191

DATE OF PUBLICATION
09 December 2008

CC14/064

Appendix B - Calmettes Nite PI

SCHEDULING STATUS Not scheduled

PROPRIETARY NAME

CALMETTES NITE TABLETS

COMPOSITION

Each coated tablet contains:
125 mg Valerian root dry extract (3–6:1, ethanol 70 % v/v), equivalent to 375–750 mg Valerian root (extract of plant root *Valeriana officinalis*).

PHARMACOLOGICAL CLASSIFICATION

A. 34 Herbals.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

In clinical studies in patients with sleep disturbances, Valerian root extract has shown to improve sleep efficiency and quality, predominantly by shortening the sleep latency and increasing the slow wave sleep proportion. Subjective sleep parameters, as assessed by means of self-rating scores and questionnaires, improved accordingly.
Valerian had no immediate hypnotic effect but rather restored sleep macrostructure. In insomniac patients, the therapeutic benefit could be observed in the first days of treatment and further increased within the next 2–4 weeks.
Furthermore, clinical studies have demonstrated that Valerian treatment relieved from symptoms of nervousness and restlessness. Frequently associated problems like deficiencies in the concentration ability and motor restlessness were markedly improved in adults and children.

Pharmacokinetic properties

No human data on absorption, distribution, metabolism and excretion are available in the literature, and no pharmacokinetic studies have been performed on extract of Valerian root. However, the observed clinical efficacy and the toxicological studies indicate absorption and suggest that neither toxic metabolites are formed nor toxic constituents of the extract accumulate.

INDICATIONS

Calmettes Nite is a herbal medicinal product indicated for the relief of temporary mild nervous tension and temporary difficulty in falling asleep.

CONTRA-INDICATIONS

Not recommended for patients with hypersensitivity or idiosyncrasy to root of valerian or any of the excipients.

DOSAGE AND DIRECTIONS FOR USE

Adults and children over 12 years of age

As an aid to sleep, a single oral dose of 3–5 coated tablets (equivalent to 1125–3750 mg valerian root) half an hour before bedtime, with an earlier dose during the evening, if necessary.
For relief of nervous tension, a single oral dose of 3–5 coated (equivalent to 1125–3750 mg valerian root) 1–3 times daily.

Elderly

As for adults.
The coated tablets should be swallowed with fluids and not be chewed.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

No adverse effect is known to date under the recommended conditions of use.

Precautions

Since only limited clinical experience is available, the use of Calmettes Nite in children younger than 12 years of age is not recommended.
As it may enhance the central nervous depressing effects of alcohol, hypnotic, anxiolytic, narcotic, sedative and tranquilizing agents, CALMETTES NITE should be used with caution when co-administered with these agents.
CALMETTES NITE should be used with caution in patients with a history of severe liver dysfunction or severe liver disease.
Since data on the use during pregnancy and lactation are not available, the use of CALMETTES NITE is not recommended as a general precaution.
Intake of CALMETTES NITE immediately (up to two hours) before driving a car or operating machinery is not recommended.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Valerian root at a dose of approximately 20 g caused mild symptoms (fatigue, abdominal cramp, chest tightness, lightheadedness, hand tremor and mydriasis) which disappeared within 24 hours. If symptoms arise, treatment should be supportive.

IDENTIFICATION

White, round, biconvex coated tablet.

PRESENTATION

PVC/PVDC blister strips in cartons of 25 coated tablets.

STORAGE INSTRUCTIONS

Store below 25 °C, in a dry place.
KEEP OUT OF REACH OF CHILDREN.

NAME AND BUSINESS ADDRESS OF THE APPLICANT

Abbott Laboratories S.A. (Pty) Ltd
219 Golf Club Terrace
Constantia Kloof
1709

DATE OF PUBLICATION OF THIS PACKAGE INSERT

25 April 2004

Namibia: 04/2.6/1105

Appendix C – Wellvita St John's wort PI

SCHEDULING STATUS SO

PROPRIETARY NAME AND DOSAGE FORM
St. JOHN'S WORT (capsule)

COMPOSITION
Each capsule contains: Active ingredients: St. John's Wort powder *(Hypericum perforatum)* 300 mg and St. John's Wort extract (*Hypericum perforatum*) [hypericin 0,3 %] 175 mg.
*Capsules are free of gluten, preservatives, sugar and lactose.

PHARMACOLOGICAL CLASSIFICATION
D 32.2 Other.
Discipline: Western herbal.

INDICATIONS
This product is used to relieve a slightly low mood and mild anxiety. This is based on traditional use only.

CONTRA-INDICATIONS
Do not use this use in medicine if you are hypersensitive (allergic) to any of the ingredients in the formulation; or if you are pregnant or breastfeeding. Not suitable for use in children under the age of 18 years, or for longer than one year continuously, unless under medical supervision. Avoid use in patients with Alzheimers disease or any mental illness.

WARNINGS AND SPECIAL PRECAUTIONS
If you suffer from any serious ailments or conditions; or if you are taking any prescribed medication, please check with your healthcare provider before taking this medicine.
- This medicine might slow blood clotting and should be used cautiously with any other blood thinning medication. Discontinue use two weeks prior to any scheduled surgery.
- Use cautiously if you have sensitive skin as this medicine might cause photosensitivity. Sunblock should be applied while taking this medicine.
- Do not suddenly stop taking this medicine, the dosage should be decreased over a period of time. Please consult your healthcare provider for further advice.
- This medicine can cause dizziness and can influence your ability to drive and use machines. Please exercise care when driving or operating machinery until you know how it affects you.
- Porphyria: Safety has not been established.

Nutritional supplementation should not replace a balanced diet. Do not exceed the recommended dose without consulting a healthcare provider.

PREGNANCY AND LACTATION
If you are pregnant or breastfeeding, please consult your doctor, pharmacist or other healthcare provider for advise before taking this medicine.

INTERACTIONS
If you are taking other medicines regularly, including complementary or traditional medicines, or start taking any additional medicines while taking this medicine, consult your healthcare provider for advice. This medicine may interfere with the way the body processes certain drugs using the liver's 'cytochrome P450' enzyme system. As a result, the levels of these drugs may be altered in the blood, and may cause a decrease in efficacy or potentially serious adverse reactions. Anyone using any other medications (for example 5-HTP, warfarin, carbamazepine, phenobarbital, HIV medicine, digoxin, oral contraceptives, SSRI's, Lithium, epilepsy medicine etc.) should check with their healthcare provider about possible interactions before taking this medicine. This medicine may also increase the risk of photosensitivity. Use cautiously in people with sensitive skin or those taking photosensitizing drugs.

DOSAGE AND DIRECTIONS FOR USE
Take one capsule twice a day with meals, or as directed by your healthcare provider.

SIDE EFFECTS
Side effects may include gastrointestinal symptoms, dizziness, headache, confusion, mania, increased urinary frequency, allergic reactions, fatigue, photosensitivity, trouble sleeping and dry mouth. Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, discontinue use immediately and consult your doctor, pharmacist or other healthcare provider for advice.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
No known symptoms of overdose. Treatment is symptomatic and supportive.

IDENTIFICATION
White capsule.

PRESENTATION
60 Capsules are packed in a plastic container.

STORAGE INSTRUCTIONS
Store all medicines out of reach of children. Store in a cool dry place below 25 ˚C and keep away from direct sunlight. Keep the container tightly closed.

NAPPI CODE
721451001

REGISTRATION NUMBER
To be allocated.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE
Alveta Healthcare (Pty) Ltd, 18 Greenwich Grove, Station Road, Rondebosch, 7700. Company registration number: 2004/021899/07. Pharmacy audit number: Y53008.

DATE OF PUBLICATION OF THE PACKAGE INSERT
30 September 2013

WSTJO/OCT16

This medicine has not been evaluated by the Medicines Control Council.
This medicine is not intended to diagnose, treat, cure or prevent any disease.

Appendix D: Flora Force St John's wort capsules PI

C0 Flora Force St John's wort Capsules 300mg

Scheduling status: C0

Proprietary name (and dosage form): Flora Force St John's wort Capsules 300mg.

Composition: Each capsule contains Hypericum perforatum powder 300mg.

Pharmacological classification: Category D Western Herbal Medicine

Pharmacological action: 1.2 Central Nervous System Stimulants, Psycho-analeptics (Antidepressants)

Indications: Herbal medicine for the treatment of anxiety, nervous stress and mild depression.

Contra-indications: Do not use with MOA inhibiting, or SSRI drugs and oral contraceptives, theophylline, simvastatin, and anti-histamine.
Do not use when pregnant or breastfeeding.

Warnings: Discontinue use 3 days before any general anaesthetic and surgery.
Photo-sensitivity, avoid any exposure to ultraviolet lights and full sun.
Persons on SSRI drugs should not take St John's wort (*Hypericum perforatum*). Discuss with medical practitioner.

Drug Interactions:
Warfarin, ciclosporin, digoxin, theophylline and anti-convulsants. HIV protease inhibitors and HIV non-nucleoside reverse transcriptase inhibitors. Oral contraceptives, Triptans and SRRI

Pregnancy and Lactation: Should not be used during pregnancy and lactation.

Dosage and directions for use: Take one to two capsules twice daily. Should the condition not improve within 4 weeks, please consult your practitioner.

Side-effects and special Pre-cautions: Photosensitivity and gastro-intestinal symptoms.

Known symptoms of over dosage and particulars of its treatment: Gastro-intestinal discomfort.
Treatment is symptomatic and supportive.

Identification: Clear size 0 vegetable capsule containing brown to dark brown herbal powder.

Presentation: 60 Capsules packed into 125ml amber glass bottle with light green screw cap and safety seal insert

Storage instructions: Store below 25°C. KEEP OUT OF REACH OF CHILDREN

Registration number: To be allocated

Applicant:
Flora Force Health Products (Pty) Ltd.
P.O. Box 426, Rondebosch, Cape Town, 7701.

Date of Publication: 17/06/2015

Appendix E: Sample of Biral PI Data Collection Sheet

Data Collection Sheet:

References:

- Guideline 2.14_PIL_Dec 14_V4
- Guideline 2.16_PI_for_human_medicines_Dec 13_V5

Product name: _Biral® Sugar coated tablets_____ **PI available: YES/NO** **PIL available: YES/NO**

Standard PI format Requirements:

Requirements listed in Italics are explanatory or instructive notes

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
Scheduling Status	The Scheduling Status as determined by Council and published in the Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended.	Present	S0	N/A
Proprietary Name and Dosage Form	The proposed proprietary name as approved by Council.	Biral ® sugar coated tablets		N/A
Composition	Use the INN name, include all excipients present in the final product. Include the warning: "contains sugar" or "sugar – free" as applicable. Where there is a sugar known to have intolerance or side effects, the presence of this sugar should be reflected e.g., "Contains Lactose monohydrate".	Partially completes	"contains sugar" included. Excipients have not been included in the PI, only in the PIL.	N/A
Pharmacological classification	In accordance with Regulation 9.1(d) and Regulation 25, the Medicines and Related	Present	A 2.6 - Tranquilisers	N/A

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	Substances Act, 1965 (Act 101 of 1965), as amended.			
Pharmacological Action	Only what is relevant to the prescriber, taking into account the approved therapeutic indications and potential adverse reactions.	Present	"Valerian and Passiflora are natural products of plant origin, which act on the central nervous system to bring about a mild sedative action."	Khoma *et* al (2007) and Becker *et al* (2014) showed Valerenic Acid, the apparent active constituent of Valerian root (Becker *et al*, 2014) potentiates and inhibits $GABA_A$ receptors, contributing to valerian roots anxiolytic and sedative properties.
Pharmacodynamic properties	Describe mechanism of action (if known), pharmacodynamic effects, relevant clinical efficacy.	Absent	No information available	
Pharmacokinetic properties	Pharmacokinetic properties of the active substance(s) relevant for the recommended dose and for the strength and pharmaceutical formulation marketed should be given. This should include reference to absorption, distribution, protein binding, biotransformation,	Absent	No information available	

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	elimination and linearity/non-linearity, as appropriate for the medicine marketed. Include information on the intake of the medicine in relation to food intake (i.e. with or without food). Include characteristics in specific patient groups with respect to factors such as age, gender, smoking, polymorphic metabolism and concomitant pathological situations such as renal impairment and hepatic insufficiency, when clinically relevant. Information on pharmacokinetic and pharmacodynamic relationship(s) and the contribution (if any) of metabolite(s) should be included, where relevant.			
Summary of Clinical Studies	Only on request of the MCC	Absent	No information available	
Indications	The indication should be stated clearly and concisely and define the target disease distinguishing between treatment, primary prevention, secondary prevention and diagnostic indications. When appropriate it should define the target population and/or the duration of treatment (i.e. short or long term)	Present	Anxiety, restlessness and minor neuroses characterised by the absence of depression.	"Relieve nervousness; used as a sleep aid/promote sleep" (Canadian monograph for Valerian root)
Contraindications	Absolute contraindications; this could include particular clinical diagnoses, concomitant diseases, demographic	Present	"hypersensitivity to any of the ingredients. There	"No statement is required" (Canadian

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, prior adverse reactions to the medicine or class of medicines). Where the use of a medicine may be life-threatening, cause mortality or serious morbidity. Medicines or classes of medicine of which the concomitant or consecutive use should be contraindicated, based on data or where there are strong theoretical reasons for not using the combination. (Cross-reference to INTERACTIONS.) If a safety issue can be predicted in a patient population (e.g. use of a renally cleared substance with narrow therapeutic margin in renal failure patients), or if patients were excluded from studies as being contraindicated on serious grounds of safety. Pregnancy and/or lactation, if absolutely contraindicated. (Cross-reference to PREGNANCY AND LACTATION) Hypersensitivity to any of the ingredients, including excipients. Porphyria, if absolutely contraindicated. (See WARNINGS.)		are no known contra-indications."	monograph for valerian root).

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
Warnings and Special Precautions	Specific safety issues, especially those that may lead to death or serious harm, may be required to be placed in a prominently displayed box and/or bolded font. Relative contraindications: Conditions under which use of the medicine could be acceptable, provided that special conditions for use are fulfilled. Special patient groups likely to experience medicine or class related adverse reactions under normal conditions of use. Serious adverse reactions to which the prescriber needs to be alerted, the situations in which these may occur and the actions that may be required. Any need for awareness of symptoms or signs representing early warning of a serious adverse reaction, and any need for specific clinical laboratory or other monitoring. If dose reduction is recommended in such circumstances, this should be included under DOSAGE AND DIRECTIONS FOR USE and cross-referenced in this section. Clinically relevant interactions. Cross reference to Side Effects and Pregnancy and Lactation.	Absent		

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	Effects on ability to drive and use machines. Porphyria: If not shown to be safe only the statement "Safety has not been established" will be allowed. Measures to be taken to avoid specific adverse reactions should be mentioned here. This includes reactions referred to under Side Effects, as well as any other adverse events which may occur. Any special precaution necessary relating to excipients.			
Interactions	Include information on potentially clinically relevant interactions based on the pharmacology of the medicine, particularly on interactions which result in a recommendation regarding the use of the medicine. The order of presentation should be contraindicated combinations, those where concomitant use is not recommended, followed by others. Interactions affecting the use of the medicine concerned (in the package insert) should be given first, followed by interactions resulting in clinically relevant changes on the use of other medicines. Interactions referred to in other sections of the package insert should be outlined and cross-referenced to the other sections.	Present	"No known interactions"	

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	The following information should be given for each clinically relevant interaction: • contraindication of concomitant use (cross reference to CONTRAINDICATIONS) • concomitant use not recommended (cross-reference to WARNINGS) • precautions regarding dose adjustment (cross reference to DOSAGE AND DIRECTIONS FOR USE and to WARNINGS), stating specific situations where these may be required. • For the actual dose recommendation, refer to DOSAGE AND DIRECTIONS FOR USE. • any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters • mechanism if known • the period of interaction if discontinuation of a medicine requires adjustment of the doses of concomitant (interacting) medicines, e.g. if a medicine is an enzyme inhibitor or inducer • the need for a washout period when using medicines consecutively. Interactions not studied *in vivo*, but predicted from *in vitro* studies or deducible from other situations or studies should be described if they could result in a change in the use of the			

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	medicine, cross-referencing to DOSAGE AND DIRECTIONS FOR USE and/or to WARNINGS. Information on other relevant interactions such as with food or pharmacologically active substances not used for medical purposes. Include interactions with laboratory tests and investigations. If no interactions studies have been performed, this should be stated.			
Pregnancy and Lactation	Facts on human experience and conclusions from preclinical toxicity studies, which are of relevance for the assessment of risks associated with exposure during pregnancy. (Cross-reference to CONTRAINDICATIONS as appropriate.) Recommendations on the use of the medicine at different times during pregnancy in respect of gestation. Statements such as “where the benefit outweighs the risk” or “at the discretion of the medical practitioner” or “should not be used unless clearly necessary” will not be allowed. When no information is available, the statement “Safety and/or efficacy has not been established” will be allowed.	Present	‘Safety during pregnancy and lactation has not been established.’	

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	Recommendations on the management of the situation of an inadvertent exposure, where relevant.			
Women of Childbearing Potential	Recommendations on the use of the medicine in women of child-bearing potential, including contraception and testing for pregnancy, should be stated, when appropriate. It should be indicated if alternative contraception is required for patients and for their partners, during treatment and for a defined period after treatment, as appropriate. (Cross-reference to CONTRAINDICATIONS or any other section, as appropriate.)	Absent		
Lactation	Information on excretion of the active substance and/or its metabolite(s) in milk. (Cross-reference to CONTRAINDICATIONS, WARNINGS or any other section, as appropriate.) A recommendation as to whether to stop or continue breast-feeding.	Absent		
Fertility	Information regarding fertility should be given in sections CONTRAINDICATIONS, WARNINGS, or SIDE EFFECTS, as appropriate.	Absent		
Dosage and Directions for use	Include, for each route of administration and for each indication: • dose and dose interval • duration of treatment where relevant; in particular, if short-term treatment is part of	Partially Present	Only adult dosage with reference to meals included. Duration, dose adjustments for age	'0.3 - 12 Grams per day dried root or root and rhizome , not to exceed 3.6 Grams per single dose' (Canadian

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	the indication, the duration of treatment should be included as part of the dosage • dosage adjustment for each age category where appropriate • dosage adjustment with renal insufficiency, liver disease, dialysis, concomitant disease or interactions requiring specific dose adjustments • monitoring advice, where applicable. • cross-referencing to other sections, as relevant. Where appropriate the following points should be addressed: • the maximum recommended single, daily and/or total dose • the need for dose titration • the normal duration of use and any restrictions on duration • if relevant, the need for tapering off • the intake of the medicine in relation to food intake.		or disease state, maximum daily dose not included. '*Adults*: Unless otherwise directed, initially two tablets should be taken with water three times daily after meals. After improvement or in less severe case, one tablet should be taken three times daily after meals.'	monograph for valerian root). Recommended dose is 2 tablets (200mg) three times per day (600mg) therefore falls into recommended range for all standardised extracts for Valerian root. No statement on duration of use is required as per Canadian Monograph.
Side Effects	This section should provide comprehensive information based on all adverse reactions from clinical trials, post-marketing studies or spontaneous reports attributed to the medicine. Include all adverse reactions if they are at least possibly causally related. **Information obtained from clinical trials/studies and**	Present	'Adverse reactions with normal therapeutic doses are unknown. Should any adverse reaction occur, discontinue medication immediately.	'Some people may experience drowsiness. Exercise caution if operating heavy machinery, driving a motor vehicle or involved in activities requiring

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	from post-marketing data should be presented separately. The section should be structured according to the following recommendations: a) A brief, general description will be necessary for most medicines, providing an estimate of the overall percentage of treated patients expected to experience adverse reactions. This information must be consistent with the figures presented and must not contain general statements such as “well tolerated”, “adverse reactions are normally rare”, etc. b) Classification of adverse reactions should be according to a system organ class (SOC) for data from both pre-marketing and post- marketing sources. c) Frequency of Adverse Drug Reactions (ADRs): **For clinical trials/studies data:** Within each SOC, the adverse reactions should be ranked under CIOMS headings of frequency, most frequent reactions first, using the following convention: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1 000, <1/100); rare		Hypersensitivity has been known to occur with the use of Passiflorae extractum siccum.’	mental alertness within 2 hours of consumption’ (Canadian monograph for valerian root).

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	(≥ 1/10 000, < 1/1000); very rare (<1/10 000), including isolated reports. Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness, as determined from clinical studies. For pooled data from clinical trials/studies, the frequency category representing the highest frequency should be used. Tabulation of adverse reactions according to a SOC may also be used. Presentation of ADR information relative to placebo should be presented as absolute percentages (not as placebo subtracted). **For data from sources other than clinical trials/studies data**: When the frequency of occurrence of adverse events is not available from clinical studies, the terms "frequent" or "less frequent" should be used. The following guide should be applied for frequency information obtained from sources other than clinical trials: 'more frequent', 'very common' and 'common' ≡ 'frequent' 'single reports' or 'isolated reports', 'uncommon', 'rare', 'very rare' ≡ 'less frequent'.			

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	The term reporting the highest frequency should always be used and all information must be clearly referenced. The appropriateness of the source(s) remains at the discretion of Council. When no frequency data are available for a specific ADR, the statement “frequency not known” or “frequency unknown” may be added, with justification for the lack of information and providing the reference sources consulted. **For post-marketing data:** **Spontaneous reports:** Information relating to individual serious and/or frequently occurring adverse reactions, for which there is no frequency estimation available (e.g. obtained from a spontaneous reporting system) must be included. No frequency categories can be allocated to individual reports from a spontaneous reporting system. **Post-marketing studies:** Information from post-marketing studies (e.g. phase IV studies) should be separate from that obtained from pre-marketing clinical trials, with frequency categories according to the CIOMS convention (as for clinical			

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	trials/study data), and with the study(ies) clearly identified. In the case of combination medicines, where it is known which particular adverse reactions are attributable to which component of the combination, the information should be presented separately. Any adverse reactions resulting directly from an interaction should be included and cross-referenced to Interactions. Any adverse reaction which may be related to excipients or residues from the manufacturing process should be included.			
Known Symptoms of Overdose and Particulars of Treatment	Describe acute symptoms and signs and potential sequelae of overdosage. Describe recommended management of overdose or methods to increase elimination of the medicine.	Present		
Identification	As per final product specification	Present		
Presentation	As per the specification for packaging	Present		
Storage instructions	As per the stability information, the storage temperatures must be stated, e.g. “Store at or below X °C” or “Store between X and Y °C”. Include other relevant storage instructions such as	Present		

PI Heading	Guideline Requirement	Present/Absent	Comment	Additional data/references
	"Keep in secondary container" where appropriate for light sensitive products.			
Registration Number	Allocated by Council upon Registration	Present		
Name and Business Address of the Holder of the Certificate of Registration		Present		
Date of Publication of the Package Insert	The following dates should be included: - the date on the registration certificate of the medicine - Thereafter the date of the most recently revised package insert as approved by Council.	Present		

Appendix F: Calmettes Nite Critical Discourse Analysis

Calmettes Nite Tablets Package Insert

PI Content	Analysis
Each coated tablet contains: 125 mg Valerian root dry extract (3-6:1, ethanol 70% % v/v), equivalent to 375 – 750 mg Valerian root (extract of plant root *Valeriana officinalis*).	No patient information leaflet is available, so although strictly speaking, a PI is intended for medical professionals, this is not a regulated medicine and patients are able to buy this medicine off the shelf, with no input or explanation about the product. The composition shows only the active ingredient. The use of the parenthesis and the technical dilution used in the preparation of the extract behaves as a barrier to the equivalent dose of valerian, which is considerably higher than the initial 125 mg.
	The 125 mg is placed in the foreground. The actual dose of valerian root taken per tablet is between 3 and 6 times higher than the originally stated dose of 125 mg. The dose listed below under DOSAGE AND DIRECTIONS for use specify the dose to be taken in Valerian Root, not valerian root extract. Having the dose listed per tablet, separated from the actual dose taken by the parenthesis and dilution formula will act as a barrier to most non-medical people, and discourage further reading. This may result in an inadvertent overdose. Most medical people, unless trained in herbal extracts are unlikely to understand the difference between the two dosages.
Pharmacodynamic properties In clinical studies in patients with sleep disturbances, Valerian root extract has shown to improve sleep efficiency and quality, predominantly by shortening the sleep latency and increasing the slow wave sleep proportion. Subjective sleep parameters, as assessed by means of self-rating scored and questionnaires, improved accordingly. Valerian had no immediate hypnotic effect but rather restored sleep macrostructure. In insomniac patients, the therapeutic benefit could be observed in the first days	Wording is very scientific and not written for the lay person. A lay person would not be expected to understand the following the following clause, explaining how Valerian root acts on the brain to improve sleep: "…efficiency and quality, predominantly by shortening the sleep latency and increasing the slow wave sleep proportion." The use of pharmacological terms, like "hypnotic" and physiological terms like "sleep latency", "sleep macrostructure" block the non-medically educated reader by using confounding terms. Most people

PI Content	Analysis
of treatment and further increased within the next 2-4 weeks. Furthermore, clinical studies have demonstrated that Valerian treatment relieved symptoms of nervousness and restlessness. Frequently associated problems like deficiencies in the concentration ability and motor restlessness are markedly improved in adults and children.	would stop reading, as they do not understand the subject. Does this mean that Valerian can be used to treat ADD? This is not listed as indication, but this inclusion implies that valerian root can be used to treat symptoms of ADD. The wording used suggests this will be an effective therapy. Ethically, this statement should not be included in the PI, as it has nothing to do with the indication and suggests an effective "natural' treatment for a far more complicated syndrome.
Pharmacokinetic properties No human data on absorption, distribution, metabolism and excretion are available in the literature, and no pharmacokinetic studies have been performed on extract of Valerian root. However, the observed clinical efficacy and the toxicological studies have shown indicate absorption and suggest that neither toxic metabolites are formed nor toxic constituents of the extract accumulate.	There are inconsistencies with how the PI refers to Valerian Root. In some sections (pharmacodynamics properties), the active ingredient is referred to as Valerian root extract, in others (pharmacokinetic properties) it is referred to "extract of Valerian root). By writing the active ingredient in a long, more formal way, it gives the tone of the sentence a more scientific, medical feel. "observed" – who observed these studies? The previous sentence has just said they do not have any data on the pharmacokinetic properties, however here someone has observed trials indicating absorption and inferring the safety of the product. Inferring safety without having some data to support your claim is a questionable practice. The PI is not marketing material, and should be used to instruct and guide a clinician, or patient in this case, as the PI is essentially a summary of important safety and clinical information.
INDICATIONS Calmettes Nite is a herbal medicinal product indicated for the relief of temporary mild nervous tension and temporary difficulty in falling asleep.	By putting the words 'herbal' and 'medicinal' together, the author of the PI is implying that this product is effective (as a medicine) and is safe and well tolerated by virtue of it being herbal. Instead of calling the product a herbal remedy, or even just a herbal product, the words herbal medicine are used to put the reader in the desired frame of mind, and imply safety and

PI Content	Analysis
	efficacy, even in the face of self-confessed lack of evidence. Within the section explaining the pharmacodynamic properties of Calmettes Nite, they mention that the efficacy of the product increases over 2-4 weeks. Nowhere in the insert do they specify what is considered to be temporary or mild? To many people, a month long treatment is not a temporary condition.
CONTRA-INDICATIONS Not recommended for patients with hypersensitivity or idiosyncrasy to root of valerian or any of the excipients.	Again confounding words and medical terms have been used. This was possibly done as a method of distraction or diversion away from the possibility of any negative reactions that could be associated with the use of product that is self-proclaimed to be effective, safe and non-toxic, as described above. Once again, we have inconsistencies with the way the active ingredient is named: Valerian, Valerian Root extract, extract of Valerian root, and root of valerian. The choice of words used in the contraindications sections of the PI (which one may think of as the negative section) is interesting. The sentence is clumsy and does not read easily; by writing out "Valerian root'" in a long and technical way (i.e.: root of valerian) it discourages the reader from finishing the sentence and comprehending the meaning that in fact, there are patients for who Valerian root would not be appropriate. This is further enforced by the use of the word "excipients", which only pharmaceutically trained people are likely to understand. If you cannot understand a word, you are more likely to disregard it entirely. Interestingly, although hypersensitivity to the excipients is listed as a side effect, the excipients are not listed on the PI. This is a requirement for Package Inserts as per Guideline 2.16.
DOSAGE AND DIRECTIONS FOR USE **Adults and children over 12 years of age**	

PI Content	Analysis
As an aid to sleep, a single oral dose of 3-5 coated tablets (equivalent to 1125-3750 mg valerian root) half an hour before bedtime, with an earlier dose during the evening, if necessary. For relief of nervous tension, a single oral dose of 3-5 coated (equivalent to 1125 – 3750 mg valerian root) 1-3 times daily. **Elderly** As for adults. The coated tablets should be swallowed with fluids and not be chewed.	"A single, oral dose" is a simple and clear instruction. However the inclusion of the equivalent Valerian Root dose, as opposed to the dose of the extract (if it should be included at all) creates a break in the sentence, especially when combined with the use of parenthesis. The patient can take a dose earlier in the evening if necessary, but the instructions are very vague. How much earlier (before the bedtime dose) should the extra dose be taken? Should this dose be another 3-5 tablets? Can a patient safely take that many tablets? Is there a maximum that should not be exceeded? The instructions for the relief of nervous tension follow a similar vein to that of the sleeping aid instructions, but here they provide dosing intervals. This sentence is also vague and does not provide clear instruction. Why have they provided the equivalent dose of valerian root, if there is no maximum dose to be aware of? Should 5 tablets be taken 3 times a day? Is this safe? The pack only provides 25 tablets, this means a full pack would be finished in less than 2 days. The structure of the sentence about not chewing the tablets and swallowing them with fluids and being placed immediately underneath the instructions for the elderly gives the impression that this instruction is meant for the elderly alone, but not for adults and children.
<u>SIDE EFFECTS AND SPECIAL PRECAUTIONS</u> No adverse effect is known to date under the recommended conditions of use. **Precautions** Since only limited clinical experience is available, the use of Calmettes Nite in children younger than 12 years of age is not recommended. As it may enhance the central nervous depressing effects of alcohol, hypnotic, anxiolytic, narcotic, sedative and tranquilising agents, CALMETTES NITE	"Known to date" implies current knowledge, but when last was this package insert updated? The published date is 2004, surely this could have been updated since then? Again, the lack of data proving safety is admitted in the package insert. The sentence structure is clumsy and in the passive voice, which makes sentences longer and discourages reading the

PI Content	Analysis
should be used with caution when co-administered with these agents. CALMETTES NITE should be used with caution in patients with a history of severe liver dysfunction or severe liver disease. Since data on the use during pregnancy and lactation are not available, the use of CALMETTES NITE is not recommended as a general precaution. Intake of CALMETTES NITE immediately (up to two hours) before driving a car or operating machinery is not recommended.	sentence to the end to get all the information. The use of medical and pharmacological terms complicates the sentence unnecessarily. A lay person will probably not know what medicines may be hypnotic, anxiolytic, narcotic, sedatives or tranquilising, and as a result, not be aware that they should not be taken or used with caution when taking Calmettes Nite. Use of the word "co-administered" when read by patient implies the responsibility for taking the medicines is someone else's responsibility. Patients take medicine, but a doctor or nurse will administer a medicine to a patient. There is a huge lack of accountability for one's health among patient and the poorer, less educated population. Sentences like (if read by a patient) enforce that notion. If a patient with severe liver disease or dysfunction wanted to take this product, they would have had read all the way to this point, near the bottom of the insert before discovering this contra-indication. This section would have been better to include in contraindication, near the top of the PI. Liver dysfunction is also a very broad term that could mean a number of things. To a patient, how is liver dysfunction different to liver disease? How severe must the liver disease be before you can't take this product? One would hope that a patient who does have severe liver disease has been adequately counselled by his doctors to know what medicines, herbal and western, can be used. While data in pregnancy is hard to source, even for western medicines with full clinical data, this is the third time that the package insert has said there is limited data available. Immediately, and up to two hours are quite separate things for a lot of people. Not

PI Content	Analysis
	many people would consider a two hour wait immediate. By putting "up to two hours" in parenthesis, it can raise questions for a first time user of the product, who may not know what effect the product will have on them. Because this product is indicated for anxiety and nervousness, and can be taken three times per day, the package insert contradicts itself throughout the text.
<u>KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT</u> Valerian root at a dose of approximately 20 g caused mild symptoms (fatigue, abdominal cramp, chest tightness, lightheadedness, hand tremor and mydriasis) which disappeared within 24 hours. If symptoms arise, treatment should be supportive.	At the highest current recommended dose, a patient could consume 11.25 g of valerian root, and if a patient had to consume all 25 tablets in the pack, they would ingest 18.75 g which is within the limit described in this section of the PI. Once again we find the use of medical terms within parenthesis, which could have been inserted in an effort to downplay the severity of symptoms. Also, these symptoms could all be symptoms of a panic attack, or be experienced by a highly anxious person. It would be impossible for a person in a state of high anxiety to distinguish between a possible overdose of valerian root (there are many forms of valerian root available over the counter, in many different combinations) and the effects of a panic attack or panic state.

Appendix G – HREC Approval

Please see Wits Human Research Ethics Committee Clearance Certificate number M160439 attached hereto.

R14/49 Miss Catherine Forbes

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160439

NAME: (Principal Investigator)	Miss Catherine Forbes
DEPARTMENT:	Pharmacy and Pharmacology University of the Witwatersrand
PROJECT TITLE:	A Comparison of the Information used to Populate Patient Information Leaflets for Complementary Medicines with Recommended References, and an Analysis of the Type and Order of language Used
DATE CONSIDERED:	06/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Neil Butkow
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/05/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially review in April and will therefore be due in the month of April each year.

Principal Investigator Signature

Date 13/8/2019

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES