COMPARISON OF PACKAGE INSERTS AND PATIENT INFORMATION LEAFLETS: AN IN-DEPTH ANALYSIS OF PRESCRIBING INFORMATION IN ANGIOTENSIN RECEPTOR BLOCKERS MARKETED IN SOUTH AFRICA

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DECLARATION

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

_____

(Signature of candidate)

_____day of_____20_____in_____

Dedicated to

My mother, Razia Aziz,

who has always been my pillar of strength.

ABSTRACT

Lack of information has been identified as a major factor as to why patients do not take their medicines as the prescriber intends. Provision of appropriate information in a suitable form is therefore crucial. The package insert (PI) is the document that ensures the safe and effective use of the medicine under most circumstances. It presents a scientific, objective account of the medicine's use as established by pre-clinical, clinical and often post-marketing studies. The patient information leaflet (PIL), which contains information for the consumer should be less scientific. South African legislation states that information contained in PILs must be aligned to PIs but the text must be readily intelligible for the patient. The study included a detailed comparison of prescribing information contained in the PI compared to the PIL in selected Angiotensin Receptor Blockers (ARBs). Findings of this comparative analysis revealed that key safety information was omitted from the PILs. An evaluation of the readability of the PILs was also performed by the use of Fry's readability formula as well as applying elements of critical discourse analysis to determine if the texts in the PILs are suitable for its purpose. The results of the Fry's readability assessments of all the PILs indicated that they had exceeded the recommended grade 7 reading level, which is in line with the adult literacy rate that qualifies anyone older than 15 years with a grade 7 qualification as being literate. Findings from the critical discourse analysis of the PILs show frequent use of medical jargon, complex sentence construction as well as ambiguity and slippage in the meaning of the texts in the PILs. The texts are not patient-friendly. Overall, the findings from this study indicate an urgent need to address the poor construction of PILs, to ensure that patients receive appropriate written prescribing information. This will ultimately ensure the safe and effective use of the medicine.

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III. NOMENCLATURE

PI:	Package Insert
PIL:	Patient Information Leaflet
MCC:	Medicines Control Council
ARB:	Angiotensin Receptor Blocker
CPA:	Consumer Protection Act
EU:	European Union
US:	United States
UK:	United Kingdom
FDA:	Food and Drug Authority

CHAPTER 1: INTRODUCTION

Medication use is widespread in our modern society. Cornerstones of effective medication use is efficacy and safety. The correct and appropriate use of medication is transmitted through the package insert (PI). The PI is a legal document that must accompany all dispensed medication and contains vital information on each medication. Lack of accurate information has been identified as major factor for why patients do not take medicines as the prescriber intends[1].

In the 21st century, patients are no longer passive and subservient but have almost unlimited access to a wide spread of information through the internet. Many of the most common and popular Google searches involve medical terms. Not all of this information is derived from reputable sources. Patients are encouraged to take greater personal responsibility, for health care decisions and thus, access to high quality information is essential if medicines are to be used safely and effectively[2]. Patient information pertaining to medication communicated verbally by the healthcare practitioner (i.e. doctor, nurse or pharmacist) has its limitations. Research has indicated that, on average, patients had forgotten half of what they had heard from the doctor within five minutes of leaving the consultation room[1]. Thus, providing good quality written information to patients is critical.

Health care professionals are inundated with product information by pharmaceutical companies but this activity is highly regulated and subject to a mandatory marketing code of conduct. The information that the pharmaceutical companies are legally allowed to disseminate is found in abbreviated form in the package insert. The package insert is also referenced in the compendium of medicines like MIMS. The veracity of this information is absolutely vital to ensure the effective use of scheduled medication. The package insert (PI) is one interface between the pharmaceutical company, the provider of health care and the ultimate utilizer, the patient. The PI contains information that ensures the safe and effective use of the medicine as indicated. PIs contain a summary of the clinical information associated with the use of medicine in the clinical trial domain and post-marketing studies[3,4].

PIs are structured with headings such as indications, contraindications, dosage and directions for use, side effects and special precautions. Populating the PI under these headings is usually accomplished with information that is more closely aligned to the health care practitioner than the patient. As a result, the technical terms and information may only be understandable by health care practitioners. Consequently, patient information leaflets (PILs) are often included. The PIL should contain information that is pitched at a patient that is a lay person (with no health care background) and is defined as: “any document that describes the characteristics, dosing methods, and adverse effects of a specific medication, is consistent with prescription drug labelling standards, and is written in consumer-oriented lay language”[5]. As the PIL is regarded as the consumer medicine information, the language used in this document should ideally be less scientific than the PI but still reflect the content.

1.1 South African Legislation

The Medicines and Related Substances Act (Act no. 101 of 1965)[6] and the general regulations made in terms of the Medicines and Related Substances Act (Act no. 101 of 1965), address the legal requirements that a PI and PIL be present in every medicine package. Regulations 9 and 10 of Act 101 stipulate the minimum information requirements of the PI and PIL. Further to this, the Medicine Control Council (MCC) of South Africa has determined a format for the PI and PIL as well as published detailed guidelines pertaining to the type of information that should appear in these documents[3,4]. The MCC have also included in guidelines, standardised texts for a given drug/therapeutic class which form the minimum key information to appear on the scientific package insert for a particular drug or class of drugs[7]. Both the PI and PIL should be available in English as well as one other official language. Although the legislation does not specify which other official language should be used; Afrikaans is commonly utilised by most pharmaceutical manufacturers.

The MCC evaluates and controls the content of each package insert and patient information leaflet at the time of registration of all scheduled medicine. Ideally, in the post-registration phase of the medicine, package inserts and patient information leaflets should be periodically reviewed and updated in accordance with the latest safety information.

Research based pharmaceutical companies generally comply with this requirement to update their prescribing information periodically in line with EU and US requirements, based on phase IV clinical trial data, pharmacovigilance activities and ongoing research[7].

Pharmaceutical companies are legally bound to compile package inserts and patient information leaflets that meet with the legislative requirements, fit into the drug packaging and are understood by a general population with diverse abilities and needs, typical of the South African population[8]. This is further reinforced by the National Consumer Protection Act, urging companies across most sectors to address consumers in a manner that is easily understood by the general population. Most pharmaceutical companies do not fully comply with this requirement, continuing to use highly technical terms in the PILs[5]. The implementation of the Consumer Protection Act 68 of 2008 (CPA) is designed to protect consumer rights if it is administered and resourced appropriately[9]. In terms of CPA, the patient is regarded as a consumer, medicines as goods and consultations offered by healthcare professionals as services[9]. The CPA enforces strict liability for harm caused by services and goods, including medicines. In the event of harm (no-fault liability) being suffered as a result of the supply of any unsafe goods, product failure or inadequate instructions or warnings pertaining to hazardous use of any goods, the producer/importer/distributor/retailer is liable, irrespective of whether there was negligence on the part of any of those persons[9].The far-reaching consequences of the CPA are yet to be realized by the pharmaceutical industry in South Africa[9].

Current legislation calls for both the PI as well as a PIL to be present in the medicine pack. However, some pharmaceutical manufacturers are still not compliant with this requirement, as it is often found that medicine packs contain no PILs. Hence, the PI is often the only medicine information available to the patient upon receipt of the medicine.

1.2 The Structure and Layout of the Patient Information Leaflet (PIL)

The format, language and legibility of PILs in South Africa is determined by the guideline published by the MCC[4].

The general requirements pertaining to the creation of the PIL are listed below[4]:

- Concise information- lengthy sentences (i.e. more than 20 words) should be avoided. Where appropriate, bullet points should be used.
- Information in the PIL must be in compliance with the Package Insert
- In terminology understandable to the patient (layman's terminology)
- Instructions should be specific to the dosage form e.g. give/take/apply
- In accordance with the SI system
- Print size and type- information appearing in the PIL to be provided to the consumer should be printed in English (British) and in at least one other official language and in a type having a minimum legibility as defined in Regulation 10 of the Act.
- Headings and sub-headings should be made conspicuous. More than two levels of headings may impair legibility.
- An active and direct style should be used, by placing the verb at the beginning of the sentence.

The MCC recommends that all PILs follow the example of the model format as published in the guidelines[4]. According to South African legislation, the information contained in the PIL must be aligned to the package insert for the medicine but the text must be phrased so that it is readily intelligible for the patient. Where a specialised term is used, an explanation should be given[4]. In the process of changing certain scientific phrases/terms used in the PI into more patient friendly language for the PIL, certain critical information may be lost or the meaning changed. Misunderstanding medical information not only jeopardises the success of the treatment, but can also result in life-threatening risks. It is crucial for patients to understand the approved uses of the medicine, contraindications regarding the use of the medicine, the correct way to administer the medicine, the correct dosages, and the potential adverse effects[10]. Various international studies have shown that most patients find package inserts difficult to interpret and understand[1,2,5,8,10-15]. Hence, the importance of ensuring that a PIL is available with all medicines and that the PIL contains all the relevant medicine information, presented in a patient-friendly manner to ensure safe and efficacious use of the medicine.

In addition to prescribing guidelines relating to the structure and layout of the text contained in the PIL, the MCC guidelines and regulations also prescribe the minimum

legibility of the text. As per Regulation 1 of Act 101, "minimum legibility" means a printing in 6-point Helvetica, typeface in black ink on white cartridge paper or the equivalent thereof [16]. This font and typeface has been found to be problematic to consumers[14]. Hence, the benefits of incorporating pharmaceutical pictograms into written medicines information has also been raised[14]. A study was conducted in a low-literate South African population and it proves that medicine information incorporating pictograms was significantly better comprehended than documents containing text only, and it was the preferred format[14].

Although the current MCC guidelines for patient information leaflets do not guarantee leaflet readability, following these guidelines stringently can vastly improve the quality of leaflets. There is currently no requirement for consumer testing of the final printed MCC approved PIL prior to distribution to the public. Thus, there is no evidence to suggest that PILs produced using the current PIL guidelines cater for the enormous diversity of the South African population. Despite the PIL guidelines that are in place, we know that information contained in the PIL is still far too technical in nature and often pertinent information presented in the PI is omitted in the corresponding sections in the PIL[5].

Information contained in the PIL is critical to the safety of patients. Guidelines published by the South African health authority relating to the construction of the PIL can be confusing to pharmaceutical companies that produce the PILs. Compliance to these guidelines are not always consistent. This study examines the degree to which information transferred from the PI to the PIL is congruent, analyses the language utilised across the PIL and evaluates the overall readability of the PIL. The use of comprehensive comparative checklists, the Fry Graph Readability Formula and critical discourse analysis are tools that are utilised in this study (see Chapter 2).

1.3 Aims

The aims of this study are to investigate:

- if information contained in the selected PILs are consistent and accurate in content as compared to the MCC approved PI, and, if information is missing from the PIL, to consider what the implications of these gaps are for patients

- the extent to which the information contained in the PIL is presented in patient-friendly language.

1.4 Objectives

The objectives of this research are to:

- to determine the variability of key information in the current approved package insert compared to current approved patient information leaflet of the same drug as well as to ascertain whether information in the PIL has been clearly and accurately adapted from the scientific package insert to the “patient-friendly” PIL by means of a comparative checklist

- to determine the readability of the PIL by use of the Fry’s readability formula and to perform a critical discourse analysis of the PIL to identify potential areas of improvement.

A select group of Angiotensin Receptor Blocker PI’s and PIL’s have been investigated in this study.

CHAPTER 2: METHODOLOGY

This chapter describes the research design utilised for this research, including the justification for the study sample selection, and methods of analysis.

2.1 Study Sample

This study analyses the PIs and PILs of a selected group of medicines called angiotensin receptor blockers, which are used extensively in the treatment of hypertension.

Hypertension, also known as high blood pressure, is amongst the leading risk of mortality, responsible for 13 % of deaths globally[17]. In Sub-Saharan Africa, hypertension affects more than 27 % of people over the age of 20. By 2025, in Sub-Saharan Africa, more than 150 million people are expected to be affected by hypertension[18].

Hypertension is a common condition in South Africa, which can increase the risk for myocardial infarction, heart failure, kidney disease or stroke[19]. This is as a result of urbanisation and lifestyle, which have led to a significant increase in cardiovascular disease, particularly hypertension[19-21].

Angiotensin receptor blockers (ARBs) have become an important part of the hypertension treatment regimen. The hypertension treatment guidelines, ESH-ESC, recommends an ARB and calcium channel blocker fixed combination as an initial choice for the treatment of hypertension[22]. The superior tolerability of ARBs leads to the highest rate of persistence and compliance among antihypertensive drugs[23]. High utilization and the relatively recent appearance of this class of drugs, signify the ARBs as an example for this study.

The following criteria guided the choice of drug selection for this research:

- The class of drugs selected must be widely used in South Africa (as discussed previously, angiotensin receptor blockers are widely used for the treatment of hypertension, one of the largest non-communicable diseases in South Africa).

- The angiotensin receptor blocker products must contain a PI and a PIL in the medicine pack for inclusion in the study. Even though the provision of PILs in all medicine packs were mandated by Regulation 10 of the Medicines and Related Substances Control Act, Act 101, as amended, from May 2003 (Government Notice, Department of Health, 2003), many companies within the pharmaceutical sector have not yet complied with this requirement.
- Package inserts and patient information leaflets published in English to be used.

A total of 13 innovator and 43 generic ARBs are currently marketed in South Africa and from this the 6 highest selling ARBs that met the above criteria comprise the sample[24](see Table 1). The PIs and PILs of the ARB's and ARB containing products mentioned in Table 1 have been analysed in this study.

Table 1: Medicines utilised in this study

Product Trade name	**Active Ingredient**
Exforge®	Valsartan/ Amlodipine
Cozaar®	Losartan
Cozaar Comp®	Losartan/ Hydrochlorthiazide
Micardis®	Telmisartan
Twynsta®	Telmisartan/Amlodipine
Co-Exforge®	Valsartan/Amlodipine/ Hydrochlorthiazide

2.2 Data Collection

The information used in this study is available in the public domain. Copies of the approved package inserts and patient information leaflets of the abovementioned products were obtained from various local retail/ hospital dispensaries.

2.3 Data Analysis

2.3.1 Comparative Analysis of PI and PIL

The design for the comparative analysis of the PI and the PIL was adapted from the methodology used in a local comparative PI study[7]. In order to determine if information contained in the PILs are congruent with the information presented in the corresponding PIs, a comparative table was designed for each product, using all the statements listed in each package insert under the following package insert headings:

- Composition
- Indications
- Contraindications
- Warnings
- Interactions
- Pregnancy and Lactation
- Dosage and Directions for Use
- Side Effects and Special Precautions
- Known Symptoms of Overdosage and Particulars of its Treatment

The text under these headings in the package insert was compared to the corresponding section in the patient information leaflet. A manual comparison was conducted of the PIs and PILs, identifying whether each of the statements from the table were present (Y) or not (N). Each statement was counted and a total of statements for the entire PI was tallied. A score-card of variability was thereafter compiled for all the products[7].

It must be noted that not all the headings in the PI correspond with the headings in the PIL. The headings in the PIL are labelled in more patient-friendly language as per MCC guidelines e.g. “Composition” in the PI as opposed to “What X Contains” in the PIL, where “X” refers to the product tradename.

2.3.2 Fry's Readability Test

One of the most frequently encountered problems with written health information is the use of language at a level higher than the reading skill level of the average patient[25]. This was a finding from research in mainly developed countries. This problem is likely to be exacerbated in developing countries like South Africa, where low literacy is more prevalent[26].

According to the 2012 General Household Survey (GHS) conducted by Statistics South Africa (StatsSA), 92.9 % of South African adults (15 years and older) are literate[27]. In South Africa, the adult literacy rate is qualified as anyone older than 15 with a grade 7 or higher education qualification by the GHS. The survey found about 2.643 million people in South Africa who have some or a lot of difficultly reading, or are unable to read. This corresponds to almost 7% of the adult population. However, this measure of literacy is based on self-reported ability to read and write short sentences and can thus represent false results. It should also not be assumed that everyone with a grade 7 qualification or higher is literate as competency levels per grade pertaining to literacy and numeracy are presently extremely poor. According to the Minister of Basic Education, Angie Motshekga, "South Africa's education system is a catastrophic national crisis with 'pockets of disasters", where poor literacy and numeracy skills are a key focus[28]. This needs to be taken into account to ensure readability of medicine information for the large majority of people in South Africa. This problem is further compounded by the fact South Africa is a multilingual nation and many people are not literate in English, or their reading level in English is low. This is a problem because medicine information available in the medicine pack is often only made available in English and Afrikaans.

This study measures the overall readability of each of the PILs selected. In order to establish the level of readability of the texts in the selected PILs, Fry's readability graphs were generated. The Fry Graph Readability Formula and its associated Graph are often used to provide a consensus of readability for regulatory purposes, such as readability in

the healthcare industry, to ensure a wider portion of the population can understand and access publications with a high level of readability[29].

The Fry's readability test has successfully been utilised in several other research works within South Africa[13,14,30-32] as well as in similar studies internationally[15, 25, 33]. While the Fry readability graph requires just three 100-word text samples from varying parts of a document as opposed to the document in its entirety, and only notes the average number of syllables, it is favoured by experts including the Centers for Disease Control and Prevention[15]. Plotted on a graph, the results generate the level of readability in school grades. According to Badarudeen, "it is particularly well suited to lengthy patient materials" [15].

In this study, each section of the PIL was analysed individually and plotted on the Fry's graph. Where a section was too lengthy, exceeding the maximum of 600 words per sample, the section was divided in a manner such that all text in the section could be plotted on the Fry's graph.

The online Fry Graph Readability Tool was utilised to analyse the PILs[29].

Limitations of Readability Formula

It must be noted that while readability formula and other assessment materials provide objectivity and independence while displaying predictive validity in their analyses regarding the readability of a text, they include limitations and waivers when used[31]. In spite of the above, they have proven significant enough not to prevent their extensive use in determining the grade level of reading material, and graded reading schemes[31]. It is important to note though that the Graph is based on graded reading levels of home language speakers of English in America. The proficiency of additional language speakers is taken to be one grade behind. Although the graph is not designed for the South African context, what it does do is provide a baseline of reading proficiency. Thus, if the results from the PIL of an ARB are located at a higher grade level, one can

extrapolate that this might be beyond the level of comprehensibility for the average South African reader.

The details of Fry's readability graph limitations exceeds the scope of this study, but, stating that the model is not all encompassing necessitates the use of other methods in order to bolster evident weaknesses. Consequently, readability formula are used in conjunction with qualitative analysis with respect to the readability of text.

2.3.3 Critical Discourse Analysis

In addition to working with Fry's readability graph in this research, it is important to problematise the concept of text. Texts are not neutral but are socially constructed with ideological positions, power relations, and interests embedded in them[34]. It is for this reason that this research uses Critical Discourse analysis as a theoretical framework to analyse the selected PILs.

Discourse analysis examines the way language is used. Discourse analysis (DA), or discourse studies, is a general term for a number of approaches to analyse written or oral texts significant semiotic events. In many cases, underlying the word 'discourse' is the general idea that language is structured according to different patterns that people's expressions follow when they take part in different domains of social life. 'Discourse analysis' is the analysis of these patterns[35].

Critical discourse analysis is a deconstructive reading and interpretation of a problem or text[36]. According to Hilary Janks, "critical discourse analysis (CDA) stems from a critical theory of language which sees the use of language as a form of social practice"[34]. All social practices are linked to specific historical contexts and are the means by which existing social relations are reproduced or contested and different interests are served[34]. In the case of this study, it is important to determine if the PILs serve the interests of the patients or that of the pharmaceutical company.

Discourse analysis has in the past been predominantly utilised in English and Linguistics departments but, in recent years, has become interdisciplinary, incorporating research interests in areas as diverse as social psychology, political science, anthropology,

sociology, history and law[37]. Discourse analysis also has a place in the public health care setting in terms of both verbal communication between healthcare professionals and patients as well as written communication regarding healthcare and medicine[12,36,37]. Discourse analysis is an effective method to approach a wide range of research questions in health care, and can be particularly useful to perform textual analysis of the PI and PIL.

Aspects of Fairclough's approach to textual analysis was utilised in this study to analyse the vocabulary and grammar in the texts. The following questions from Fairclough's model of critical discourse analysis was applied to the PILs[38]:

A. Vocabulary

What *experiential* values do words have?

- Are there words that are ideologically contested?
- Is there *rewording* or *overwording*?
- What ideologically significant meaning relations (*synonymy*, *hyponymy*, *antonymy*) are there between words?

What *relational* values do words have?

- Are there euphemistic expressions?
- Are there markedly formal or informal words?

B. Grammar

What experiential values do grammatical features have?

- What types of *process* and *participant* predominate?
- Is agency clear?
- Are processes what they seem?
- Are *nominalizations* used?
- Are sentences active or passive?
- Are sentences positive or negative?

What relational values do grammatical features have?

- What *modes* (*declarative*, *grammatical question*, *imperative*) are used?
- Are there important features of *relational modality*?

Critical discourse analysis also promotes the questioning of the presence and absence of information in the PILs. The absence of information provided under certain headings in the texts provides insight into the ways in which texts are constructed and position readers.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Comparative Analyses

3.1.1 Comparative Analyses of the Package Inserts and the Corresponding Patient Information Leaflets

A manual comparison was conducted of the PIs and PILs, by means of checklist tables. Separate checklist tables were created for each of the products studied. The tables listed all information in each package insert under the relevant package insert headings, as listed in Chapter 2.

The corresponding PILs were comprehensively studied and analysed, checking whether each of the statements from the table were present (Y) or not (N) in the PIL. According to the PIL guidelines, the information contained in the PIL "must be in accordance with the Package Insert for the medicine but the text must be phrased so that it is readily intelligible for the patient"[4]. Therefore, upon performing the analysis of the PIL, a "Y" indicating presence of the statement was noted as long as the information was mentioned in the PIL, even if the technical explanation as provided in the PI was absent.

Each statement in the PI, was checked against the PIL. All statements in the PIs were counted and a total of statements for the entire PI was tallied. Due to the length and extensiveness of the checklist tables, only one checklist table is illustrated below. The checklist table for Cozaar Comp, which is the product that showed the poorest results in terms of congruency of information in the PIL, is presented in Table 2 below. Refer to Appendices 1.1- 1.5 for the checklist table for the other 5 products analysed.

Table 2: Comparative Checklist Table for Cozaar Comp

Medicine: COZAAR COMP	
INFORMATION CONTAINED IN THE PI	**PRESENCE OF INFORMATION IN THE PIL Yes (Y), No (N)**
Composition 1. Each COZAAR COMP Tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide. 2. COZAAR COMP contains 4,24 mg (0,108 mEq) of potassium. 3. COZAAR COMP contains lactose hydrous.	**WHAT COZAAR COMP CONTAINS** Y N Y
Information Agreement with PIL (%)	= 2/3 = 0.67 x 100 = 66.7 %
Indications 1. COZAAR COMP is indicated for the treatment of hypertension in patients established on identical doses of the individual agents.	**WHAT COZAAR COMP IS USED FOR** Y
Information Agreement with PIL (%)	= 1/1 = 100%
Contraindications **1.** Sensitivity to any of the components of COZAAR COMP. 2. A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines. 3. Hereditary or idiopathic angioedema. 4. Hypertrophic obstructive cardiomyopathy (HOCM). 5. Severe renal function impairment (creatinine clearance < 30 ml/min). 6. Bilateral renal artery stenosis. 7. Renal artery stenosis in patients with a single kidney. 8. Aortic stenosis. 9. Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.	**Do not take COZAAR COMP:** Y Y Y Y Y Y Y Y Y Y

10. Porphyria. 11. Thiazide diuretics in (fixed dose) combination with COZAAR COMP, should not be given to patients with Addison's disease. This therapy is also contra-indicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines. 12. Lithium therapy: Concomitant administration with COZAAR COMP may lead to toxic blood concentrations of lithium. 13. Pregnancy and lactation (see **"PREGNANCY AND LACTATION")** 14. Hepatic impairment. 15. Paediatric Use: Safety and efficacy in children has not been established.	Y Y Y Y Y Y
Information Agreement with PIL (%)	= 15/15 = 100%
Warnings None	**Take special care with COZAAR COMP** N/A (Information from this section evaluated against Special Precautions section of PI only)
Information Agreement with PIL (%)	N/A
Interactions **Losartan Potassium** 1. In clinical pharmacokinetic trials no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (see "Hydrochlorothiazide, Alcohol, barbiturates or narcotics" below) ketoconazole and erythromycin. Rifampin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated. 2. Concomitant use of medicines that block angiotensin II or its effects and potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. 3. Lithium excretion may be reduced (see "CONTRA-INDICATIONS"). 4. Non-steroidal anti- inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive medicines.	**Taking other medicines with COZAAR COMP** N N Y

5. Therefore, the antihypertensive effect of COZAAR COMP may be attenuated by NSAIDs including selective COX-2 inhibitors.	Y
6. In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory medicines, including selective cyclooxygenase-2 inhibitors, the co-administration of COZAAR COMP may result in a further deterioration of renal function.	N
Hydrochlorothiazide	N
When administered concurrently the following medication may interact with thiazide diuretics:	
7. Alcohol, barbiturates or narcotics: Potentiation of orthostatic hypotension may occur.	
8. Antidiabetic medication (oral agents and insulin): Dosage adjustment of the antidiabetic medicine may be required.	Y
9. Other antihypertensive medication: Additive effect or potentiation.	Y
10. Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.	Y
11. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 %, respectively.	
12. COZAAR COMP should therefore be administered 1 hour before the intake of the resin.	Y
13. Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalaemia.	
14. Pressor amines (e.g. norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.	N
15. Skeletal muscle relaxants, non-depolarising (e.g. tubocurarine): Possible increased responsiveness to the muscle relaxant.	N
16. Lithium: Should not generally be given with diuretics.	N
17. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with COZAAR COMP.	Y
18. Non-steroidal anti-inflammatory medication including cyclooxygenase-2 inhibitors: In some patients, the administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.	Y
	Y
	Y
	Y

Information Agreement with PIL (%)	= 11/18 = 0.61= 61.1 %
Pregnancy and Lactation **Pregnancy** 1. When pregnancy is detected COZAAR COMP should be discontinued as soon as possible. 2. Not to be used in pregnancy as teratogenicity has been shown in experimental animals. 3. Thiazides cross the placental barrier and appear in cord blood. 4. The routine use of diuretics in otherwise healthy pregnant women is not recommended, and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. 5. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxaemia. 6. Women of childbearing age should ensure adequate contraception. **Lactation** 7. Safety in breastfeeding has not been established. 8. Thiazides appear in human milk.	**Pregnancy and breast-feeding:** Y N N N N N Y N
Information Agreement with PIL (%)	= 2/8 = 0.25= 25 %
Dosage and Directions for Use 1. The usual starting and maintenance dose of COZAAR COMP is one tablet once daily. 2. For patients who do not respond adequately to COZAAR COMP, the dosage may be increased to (100 mg losartan potassium and 25 mg hydrochlorothiazide) two tablets of COZAAR COMP once daily. 3. The maximum dose is two tablets of COZAAR COMP (or 100 mg losartan potassium and 25 mg hydrochlorothiazide) once daily. 4. The maximum antihypertensive effect is attained within three weeks after initiation of therapy. 5. COZAAR COMP should not be initiated in patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics).	**HOW TO TAKE COZAAR COMP** Y N N N N N

6. COZAAR COMP is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions"**). 7. No initial dosage adjustment of COZAAR COMP is necessary for elderly patients. 8. A higher dose (100 mg losartan potassium and 25 mg hydrochlorothiazide) should not be used as initial therapy in elderly patients. 9. COZAAR COMP may be administered with other antihypertensive agents, particularly calcium channel blockers and beta-blockers. 10. COZAAR COMP may be administered with or without food.	N N N Y
Information Agreement with PIL (%)	= 2/10 = 0.20= 20 %
Side Effects and Special Precautions **Side Effects** 1. In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with COZAAR COMP and are shown in decreasing order of frequency within body system: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100) and Rare (≥ 1/10 000, < 1/1 000) **Nervous system disorders** 2. Common: Dizziness **General disorders and administration site conditions** 3. Common: Asthenia/fatigue. 4. In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with losartan potassium and are shown in decreasing order of frequency within body system: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100) and Rare (≥ to 1/10 000, < 1/1 000) **Infections and infestations** 5. Common: Upper respiratory infection **Psychiatric disorders** 6. Common: Insomnia **Nervous system disorders**	**POSSIBLE SIDE EFFECTS** N Y Y N N N Y Y

7. Very common: Headache	
8. Common: Dizziness	N
Cardiac disorders	
9. Common: Palpitation, tachycardia	Y
Vascular disorders	
10. Uncommon: Orthostatic hypotension	N
Respiratory, thoracic and mediastinal disorders	
11. Common: Cough, pharyngitis, nasal congestion, sinus disorder	Y
Gastrointestinal disorders	
12. Common: Diarrhoea, nausea, abdominal pain, dyspepsia	Y
Skin and subcutaneous tissue disorders	
13. Uncommon: Rash	N
Musculoskeletal, connective tissue and bone disorders	
14. Common: Back pain, muscle cramps	N
General disorders and administration site conditions	
15. Common: Asthenia/fatigue, oedema/swelling, chest pain	N
Investigations	
16. Common: Hyperkalaemia, elevations of ALT.	N
17. In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with hydrochlorothiazide and are shown in decreasing order of frequency within body system: Events are classified within body system categories and enumerated in order of decreasing frequency, using the following definitions: Common (≥	
1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100), Rare (≥ 1/10 000, < 1/1 000), Very Rare (>	N
1/10 000, including isolated reports).	N
Blood and the lymphatic system disorders	
18. Rare: Thrombocytopenia	N
19. Very rare: Leukopenia, agranulocytosis, haemolytic anaemia	N
Metabolic and nutrition disorders	
20. Uncommon: Anorexia, hyperuricaemia	N
21. Rare: Hyperglycaemia	
Nervous System disorders	Y
22. Rare: Paraesthesia, headache	
Vascular disorders	N
23. Uncommon: Hypotension (including orthostatic hypotension)	
Respiratory, thoracic and mediastinal disorders	Y

24. Very rare: Respiratory distress, including pneumonitis and pulmonary oedema	Y
Gastrointestinal disorders	N
25. Uncommon: Nausea, vomiting	
26. Rare: Diarrhoea, constipation	N
27. Very rare: Pancreatitis	
Hepatobiliary disorders	Y
28. Rare: Jaundice (intrahepatic cholestatic jaundice)	Y
Skin and subcutaneous tissue disorders	N
29. Uncommon: Rash, urticaria	N
30. Rare: Photosensitivity	
31.Very rare: Necrotising angiitis (vasculitis and cutaneous vasculitis)	
Renal and urinary disorders	N
32. Rare: Glycosuria	N
	Y
The following side effects have been reported but the frequencies are unknown:	N
33. Infections and infestations: Sialadenitis	N
34. Blood and the lymphatic system disorders: Aplastic anaemia	Y
35. Immune system disorders: Anaphylactic reactions	Y
36. Metabolic and nutrition disorders: Electrolyte imbalance	Y
37. Psychiatric disorders: Restlessness	Y
38. Eye disorders: Xanthopsia, transient blurred vision	N
39. Ear and labyrinth disorders: Vertigo	N
40. Vascular disorders: Hypotension	N
41. Gastrointestinal disorders: Gastric irritation	
42. Skin and subcutaneous tissue disorders: Purpura	N
43. Musculoskeletal, connective tissue and bone disorders: Cramping, muscle spasm	
44. Renal and urinary disorders: Renal dysfunction, interstitial nephritis, renal failure	
45. General disorders and administration site conditions: Fever, weakness.	N
The following adverse reactions have been reported in post-marketing experience; they are derived from spontaneous reports for which precise incidences cannot be determined therefore, the frequency is unknown:	Y
46. Blood and the lymphatic system disorders: Thrombocytopenia	
47.Immune system disorders: Anaphylactic reactions, angioedema including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx	N Y N

and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other medicine including ACE inhibitors. **48. Musculoskeletal, connective tissue and bone disorders:** Arthralgia (reported with losartan) **49. Nervous system disorders:** Dysgeusia (reported with losartan) **50. Vascular disorders:** Vasculitis, including Henoch-Schoenlein purpura **51. Respiratory, thoracic and mediastinal disorders:** Cough **52. Gastrointestinal disorders:** Diarrhoea, vomiting **53. Hepatobiliary disorders:** Hepatitis **54. Skin and subcutaneous tissue disorders:** Urticaria, erythroderma has been reported with losartan. Photosensitivity has been reported with COZAAR COMP.	N Y N Y **Take special care with COZAAR COMP** Y
Special Precautions **Hypersensitivity** **55. Angioedema** (see **"Side Effects"**).	 Y
56. Hepatic and renal impairment COZAAR COMP is not recommended for patients with hepatic impairment or severe renal impairment (see **"DOSAGE AND DIRECTIONS FOR USE"**). 57. As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported. These changes in renal function may be reversible upon discontinuation of therapy. Other medication that affect the renin-angiotensin system, including COZAAR COMP, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with losartan; these changes in renal function may be reversible upon discontinuation of therapy.	N Y
58. Hypotension and electrolyte/fluid imbalance In patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of COZAAR COMP, or a lower starting dose should be used (see **"DOSAGE AND DIRECTIONS FOR USE"**). Periodic determination of serum electrolytes should be performed at appropriate intervals as in any patient receiving diuretics.	 Y N
59. Metabolic and endocrine effects	N N

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see **"INTERACTIONS"**). 60. Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. 61. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. 62. Thiazides should be discontinued before carrying out tests for parathyroid function. 63. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. 64. Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia. **65. Concomitant use with Lithium** Concomitant administration of lithium with COZAAR COMP may lead to toxic blood concentrations of lithium (see **"INTERACTIONS"**). **Other** 66. In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. 67. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides. **Excipient** 68. COZAAR COMP contains lactose. 69. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take COZAAR COMP. **Effects on Ability to Drive and Use Machinery** 70. There are no data to suggest that COZAAR COMP affects the ability to drive and use machines.	N Y Y Y Y Y N N
Information Agreement with PIL (%)	= 25/69 = 0.36 = 36.2 %
Known Symptoms of Overdosage and Particulars of its Treatment **Losartan Potassium**	**If you take more COZAAR COMP than you should**

1. Significant lethality was observed in mice and rats after oral administration of 1 000 mg/kg (3 000 mg/m²) and 2 000 mg/kg (11 800 mg/m²) (500 and 1 000 times** the maximum recommended daily human dose), respectively. ** Based on a patient weight of 50 kg	N
2. Limited data are available in regard to overdosage in humans.	N
3. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.	N
4. If symptomatic hypotension should occur, supportive treatment should be instituted.	N
5. Neither losartan nor the active metabolite can be removed by haemodialysis.	N
Hydrochlorothiazide	
6. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis.	N N
7. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.	N
8. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.	
Information Agreement with PIL (%)	= 0/8 = 0 %

3.1.2 Degree of Information Agreement between the PIs and PILs

A score-card of variability was compiled for all of the products studied. Table 3 below summarises the data presented in the comparative analysis between the PI and PIL for each product. The % Information Agreement was calculated by dividing the number of similarities present in the PIL by the total number of items present in the PI. Each section of the PI was measured against the PIL. An overall mean % Information Agreement was then calculated for each product.

Table 3: Summary of Degree of Information Agreement for all products used in this study

PI Headings	Information Agreement with PIL (%)					
	Cozaar	Cozaar Comp	Co Exforge	Exforge	Micardis	Twynsta
Composition	100	66.7	50	100	100	100
Indications	100	100	50	100	100	100
Contraindications	90	100	81.3	75	73.3	88.2
Warnings	0	N/A*	25.8	100	100	0
Interactions	37.5	61.1	81.3	16.7	27.3	38.9
Pregnancy and Lactation	33.3	25	37.5	30	44.4	40
Dosage and Directions for Use	36.4	20	45.5	28.6	44.4	30
Side Effects and Special Precautions	34.3	36.2	69.4	81.8	80	86.1
Known Symptoms of Overdosage and Particulars of its Treatment	0	0	0	0	0	0
Mean Overall Information Agreement with PIL (%)	47.9	45.4	49	59.1	63.3	53.7

*Absence of heading in PI

3.1.3 Key Differences and Observations for Each Section of the PI vs PIL

3.1.3.1 Composition

In 4 of the products, the information contained in the composition section of the PI was congruent with the PIL. However, in the case of Co Exforge, the PIL did not state the exact amount of the active components i.e. valsartan, amlodipine and hydrochlorothiazide, in each of the different strengths available. In the Cozaar Comp PIL, the quantity of one of the excipients contained in the medicine was absent. Crucially, the PI of Cozaar Comp as well as Cozaar was lacking in excipient listing, which is a mandatory requirement as per the MCC PI guidelines.

3.1.3.2 Indications

Congruency of information for the Indications section was observed for all products except Co Exforge, where the statement “CO EXFORGE is not indicated for the initial therapy of hypertension” was not found in the PIL. Although the basic information was present in the corresponding section of the PIL for each product, in most instances, the indications stated in the PI are not described in full detail in the PIL.

3.1.3.3 Contraindications

There are a number of omissions for this section in each of the products studied. One of the most pertinent omissions that could negatively impact the safety of the patient is the omission of the statement relating to the history of angioedema experienced with ARBs or ACE inhibitors. This contraindication is omitted in the Co Exforge, Cozaar Comp, Exforge and Twynsta PILs.

In the Exforge PI, porphyria is listed as a contraindication, however this is missing from the PIL. Any omission of information in this section is significant and renders the PIL non-compliant with the PIL guidelines, which state “*It is not acceptable to state only the common or major contraindications. Belief that a patient cannot understand a contraindication is not a*

reason for omitting it"[4]. For example, the omission of porphyria as a contraindication in the PIL simply because it is a medical condition that is difficult to explain, is not acceptable.

3.1.3.4 Warnings

Overall, the congruency of information in this section of the PI to the corresponding section of the PIL is poor for most of the products. In the case of Cozaar and Twynsta, there was 0% information agreement in the PILs of these products to the Warnings section of the PI and there were a number of omissions in this section in the Co Exforge PIL. The PIL guidelines state that it is unacceptable to include only the more common or major warnings/special precautions, all warnings/ special precautions need to be included in the PIL[6].

When comparing the Cozaar Comp PI to the PIL, it was found that the PI lacked the "Warnings" heading. This omission in the PI for Cozaar Comp raises questions about the MCC's evaluation of PIs.

Although the basic information was present in the corresponding section of the PIL for Exforge and Micardis, a full explanation of the warnings was not provided. For example, the warning relating to the use of Exforge in patients with renal impairment is not discussed in the PIL as it is in the PI. The PIL mentions that special care be taken in patients with kidney disease. One might argue that the lack of detail in this regard is acceptable, so as to not overburden the patient with information that is too technical in nature. The PIL guidelines also do not specify that full explanations be provided.

3.1.3.5 Interactions

None of the PILs were fully congruent with information in the PIs, although the Co Exforge PIL showed a high level of congruency at 81.3%. In all the PILs studied, the information contained in this section was found to be too generalised. The mechanism of drug interactions and the implication of interactions were not explained. It was very concerning to note the beginning statement of the interactions section in the Cozaar and Cozaar Comp PILs: "In general, Cozaar/ Cozaar Comp does not interact with food or other medicines you may be taking". There is discord between this first statement and the contents of the section

that follows, which mentions potential medicines that may interact with Cozaar/ Cozaar Comp. This statement is also contradictory as the PI lists a number of medicine interactions. Such a statement at the start of the section is misleading and ultimately affects patient safety, should the patient not read further on.

3.1.3.6 Pregnancy and Lactation

ARBs are well known to be contraindicated in pregnancy and lactation. Thus, omissions in this section in the PIL are crucial. All the PILs failed to mention that the use of contraceptives in women of childbearing age is critical, information which was present in the PI. The only PIL that contained information regarding adverse effects when used during pregnancy was Exforge. A brief mention of the adverse effects of use of the medicine during pregnancy should have been made in the other PILs as well.

3.1.3.7 Dosage and Directions for Use

There are a number of omissions in the corresponding section of the PILs, however, according to the guidelines, these omissions may be acceptable. As per the PIL guidelines "Instructions should usually be intelligible without explanations, so as not to overburden consumers with information."[4] The rationale for this is most likely to prevent the patient from making any changes to their dosage regimen, without consulting the doctor. However, certain information such as the maximum dosage of the medicine as well as the maximum time taken for the antihypertensive effect to be observed, should have been provided in these PILs but were omitted.

3.1.3.8 Side Effects and Special Precautions

The side effects information in the PIL for Exforge, Co Exforge, Twynsta and Micardis are comprehensive, as the degree of information agreement is between 69.4 and 86.1 %. However, the classification and explanation of frequency of side effects is not explained in any of the PILs except Micardis. In the PI, frequency of side effects is described as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000) very rare (< 1/10 000), including isolated reports, where the most frequent side effects appear first. This description of side effect frequency is a pertinent omission in the PILs. Merely stating a side effect occurs frequently or commonly is highly variable and

quantification of these frequencies is important for patients to know and understand their own potential risk for developing side effects from the medicines[4].

The Cozaar and Cozaar Comp side effects section in the PIL are inadequate. An attempt to explain the scarcity of side effect information is provided by the inclusion of the statement "Your doctor or pharmacist has a more complete list. Tell your doctor or pharmacist promptly about these or any other unusual symptoms". As per the PIL guidelines, certain standardised text should appear in all PILs. The standardised text that should appear in the side effects section of all PILs is as follows: "Not all side effects reported for X are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other healthcare professional for advice." Even though the guidelines mandates the appearance of this statement, it further recommends that side effect information should be in line with PI. The guideline is thus unclear in this regard and could potentially be the reason why such omissions are sometimes seen in side effect data in the PIL.

3.1.3.9 Known Symptoms of Overdosage and Particulars of its Treatment

All products studied are non-compliant with the PIL guidelines with regards to this section. All the PILs only contain the following standardised text from the PIL guidelines "In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre." [4] This statement is used to cover the limitations of omission in information in the PILs. However, the PIL guidelines explicitly state that the standardised text above be included as well as an explanation of signs and symptoms of overdosage that the patient is able to identify. Furthermore, necessary actions to be taken in the case of overdosage is extremely important for the patient, which is missing in the PILs.

3.1.3.10 Summary of Comparative Analysis

The information contained in the PILs were evaluated against information presented in the PI and it was found that overall the PIL contained much less information. The degree of information agreement was calculated per section of the PI compared to information in the PIL. The sections that showed the greatest degree of information agreement was the composition and indications section and the sections that showed the lowest percentage of

information agreement was the section relating to overdosage and its treatment, where 0 % information agreement was consistently noted across all the PILs.

Omission of information in certain sections are deemed appropriate, for example dosage adjustment information in renally impaired patients. However, in the vast majority of cases, the omission of information from the PILs is unacceptable and not in line with the PIL guidelines. It appears that information that is omitted may be omitted because it is viewed as too technical in nature for the patient or the pharmaceutical company may lack in expertise to explain the data in layman's terms. The omission of vital medicine information in the PIL has a direct impact on patient safety and success of their treatment.

3.2 Overall Readability of the PILs

3.2.1 Results of Fry's Graph

In order to establish the level of readability of the selected PILs, the online Fry Graph Readability Tool was utilised. Every section of each of the PILs were analysed individually and plotted on the Fry's graph. Where a section was too lengthy, exceeding the maximum of 600 words per sample, the section was divided in a manner such that all text in the section could be plotted on the Fry's graph. Refer to Appendices 2.1- 2.6 for the Fry Graphs for each product per section of the PIL.

Table 4 below presents the average readability grade level of each section of the PILs selected.

Table 4: Average Readability of PILs by U.S Grade Level

Sections of the PIL	Exforge	Co Exforge	Micardis	Twynsta	Cozaar	Cozaar Comp
What X contains	13	12	11	14	NR	NR
What X is used for	13	14	9	13	15	14
Before you take / use / are given / administered X	13*	11*	14*	14*	12*	13*
How to take / use / receive X	8	7.5*	8	7	10	9
Possible side effects	13*	15*	14*	11*	15*	NR
Mean Grade Level	12	11	11	12	13	12

*As this section exceeded the maximum number of 600 words to be plotted on the Fry's graph, the section was divided into smaller text samples and the result indicated is an average readability grade level.
X- Tradename of medicine
NR- No result, maximum number of syllables per 100 words exceeded

3.2.2 Discussion of Results from Readability Analysis

As discussed in the previous chapter, to achieve functional literacy, a minimum of Grade 7 is required. As can be seen from Table 3, readability generally exceeds the grade level these texts should be levelled at. The overall readability of all 6 PILs analyzed far exceeded the Grade 7 level, where the lowest average mean grade level achieved was 11 for Co Exforge and Micardis, and the highest a grade level of 13 for Cozaar. However, some individual sections showed readability levels as high as 15. A grade level of 15 indicates a tertiary level.

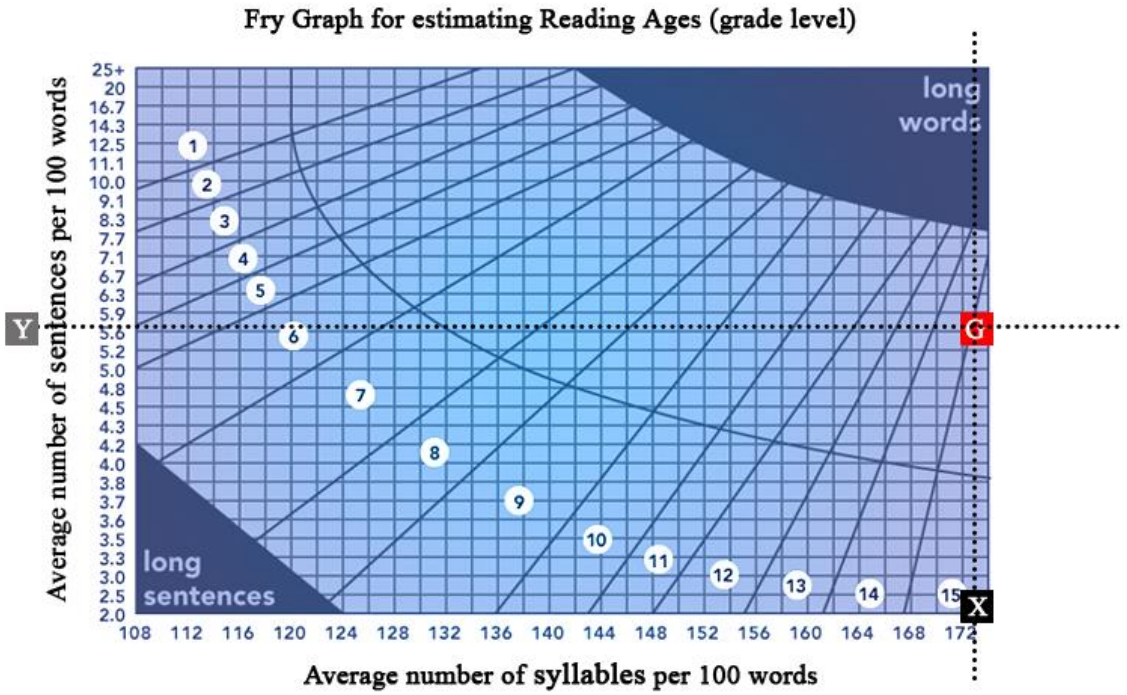
There are several factors that could be attributed to the high readability levels of the PILs. Firstly, to some extent, the use of technical medical terminology in the PIL is unavoidable. The section "What X contains" is an example. The active and inactive ingredients of the product cannot be simplified, thus high readability levels are seen for this section across all the PILs. The sections "Before you take / use / are given / administered X" and "Possible Side Effects" are also examples where the text is very technical in nature and often difficult to simplify, therefore high readability grade levels are also observed for these sections across all the PILs studied. There are instances however, where medical texts can be made more accessible without compromising on the integrity of the information. The indications section of the PI is one such example. Micardis has a readability of grade 9 level. Whilst this

is still not ideal, it is lower than the grade level of 15 for Cozaar for the same section. As both Micardis and Cozaar are ARBs and have similar indications, one would expect the readability level of both sections to be similar. Refer to the Indications section analysed from the Cozaar PIL and the related Fry's graph below:

Figure 1: Fry Graph – WHAT COZAAR IS USED FOR

Sample of text analysed from the Cozaar PIL:
"WHAT COZAAR IS USED FOR: COZAAR is an angiotensin II receptor antagonist which lowers blood pressure. COZAAR also provides kidney protection by delaying the worsening of kidney disease in type 2 diabetic patients with protein in their urine (proteinuria). Kidney disease can be measured by testing the urine for protein. Your doctor has prescribed COZAAR because you have a condition known as hypertension or high blood pressure. Your doctor may also have prescribed COZAAR because you have type 2 diabetes with protein in the urine. In type 2 diabetic patients with protein in the urine, COZAAR has been shown to slow the worsening of kidney disease."

Total # of words: 106



Interpretation of Graph derived from the online tool:

Average # of syllables per 100 words: **172**
Average # of sentences per 100 words: **5.7**

X = 172
Y = 5.7
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level

Figure 1 above illustrates that the average number of syllables per 100 words is 172, which is on the higher end of the scale. The high number of syllables in the text indicates the usage of complex words, which contributes to the high readability score for this section of the Cozaar PIL.

Another possible reason for the high readability levels of the PILs, is a lack of understanding of the target audience. Readability is closely linked to the audience. What one audience easily understands will not necessarily suit another audience[30]. Most multinational pharmaceutical companies base the South African PI and PIL on the FDA or EMA approved package inserts and patient leaflets. This practice does not take into consideration the vast difference in literacy levels between these reference countries and South Africa, where English is not the first language of the vast majority of the population. Texts in the PILs should also be culturally sensitive for it to be an effective means of communication to patients.

One may also argue that the problem of readability of the PILs lies in poor evaluations of these materials at the MCC. PILs not complying with the guidelines should not be distributed in the public domain until they are made compliant. The MCC also do not employ the use of any readability tools.

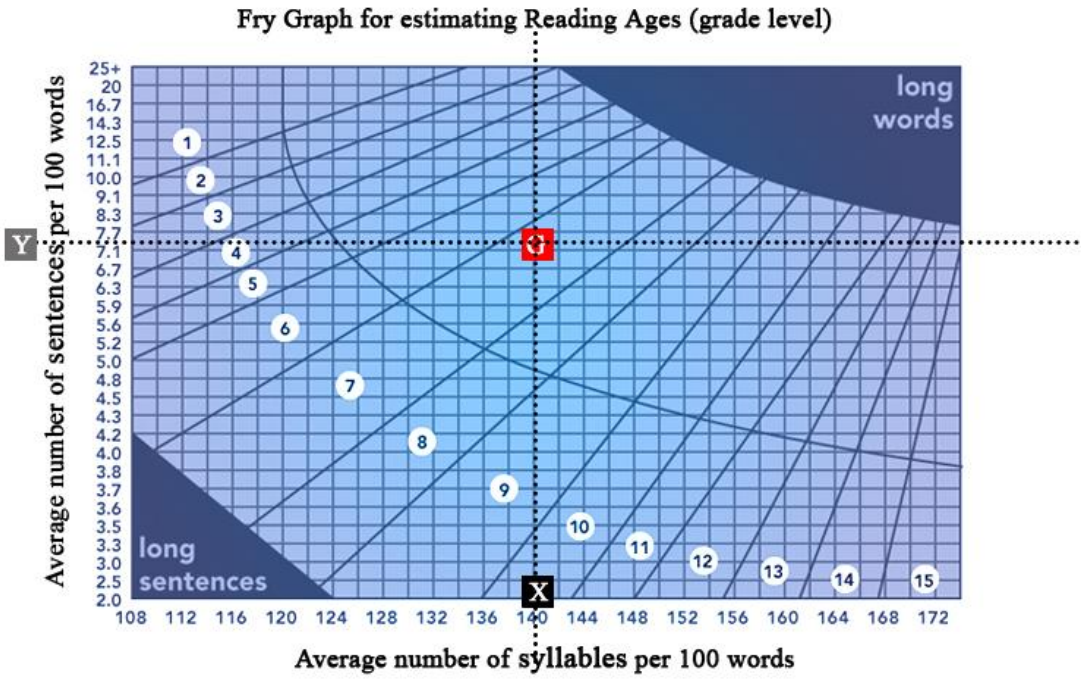
It is encouraging to note that the section “How to Take X” or dosage and directions section of the PILs, has the lowest readability grade levels. The lack of technical terms used in this section could be the contributing factor. However, from the all individual sections analysed across the 6 PILs, only one of the sections met the grade 7 level i.e. the “How to Take X” or dosage and directions section of the Twynsta PIL. Refer to the sample of text analysed from the Twynsta PIL and the related Fry’s graph below:

Figure 2: Fry Graph – HOW TO TAKE TWYNSTA

Sample of text analysed:
"4. HOW TO TAKE TWYNSTA Always take TWYNSTA exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual dose of TWYNSTA is one tablet per day. Try to take the tablet at the same time each day. Remove your TWYNSTA tablets from the blister only immediately prior to intake. You can take TWYNSTA with or without food. The tablets should be swallowed with some water or other non-alcoholic drink. It is important that you take TWYNSTA every day until your doctor tells you otherwise. If you have the impression that the effect of TWYNSTA is too strong or too weak, talk to your doctor or pharmacist. If your liver is not working properly, the usual dose should not exceed TWYNSTA 40/5 mg or TWYNSTA 40/10 mg once daily. If you take more TWYNSTA than you should: In the event of overdosage or accidental intake, consult your doctor or pharmacist. If neither is available, seek help at the nearest hospital or poison control centre. If you forget to take TWYNSTA: If you forget to take a dose, do not worry. Take it as soon as you remember on the same day. If you do not take your tablet on that same day, take your normal dose on the next day. Do not take a double dose to make up for the forgotten individual doses."

Total # of words: 235

Figure 2: Fry Graph – HOW TO TAKE TWYNSTA



Interpretation of Graph derived from the online tool:

Average # of syllables per 100 words: 140
Average # of sentences per 100 words: 7.2

X = 140

Y = 7.2

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

As simpler words are used in the sample text, the number of syllables per 100 words is 140, which contributes to the achievement of a grade 7 readability level. From this example of Twynsta, it can be concluded that it is possible to achieve acceptable readability levels, if more care is taken when constructing each section of the PIL and advice from the various international and local guidelines on simplification of text is followed more stringently.

In certain instances, it was not possible to evaluate the readability of sections of the PILs, hence “NR- no result” is represented for certain sections in the table above. This is as a result of the maximum number of syllables for the sample size being exceeded. The minimum number of words per sample size to perform the Fry’s readability analysis is 100 and the maximum is 600. The ideal sample size, using the online Fry’s readability tool, is between 300- 600 words. Even truncating a section of the PIL to select the smallest size of 100 words, did not produce favourable results using the Fry graph, as the number of syllables in the text exceeded the maximum allowable number, which is 172 syllables per 100 words. Texts with multisyllabic words are indicative of text complexity, affecting readability. Words with more than 3 syllables are classified as difficult words, thus contributing to the difficulty in reading and understanding such texts. Ideally, longer words should be replaced by shorter, more common words except where the longer word is familiar to the audience[30]. Short sentences do not necessarily increase readability as there is far more inferential work that the reader might need to do. Hence, a mix of short and longer sentences is preferable[30].

3.2.3 Summary of Readability Analysis

In conclusion, the high readability grade level observed in all the PILs studied is problematic and can seriously impact patient safety. This shows a lack of sensitivity of the pharmaceutical companies producing these texts, to the target audience and also brings into question the evaluation of PILs at the MCC.

3.3. Critical Discourse Analysis of the PILs

The aim of performing critical discourse analysis on the texts is to uncover the embedded or hidden ideological framework in texts. In the case of PILs, the language usage in the PILs is indicative of how the pharmaceutical companies, that create the PILs, position and construct patients, healthcare professionals and themselves. It has been found that PILs often fail to meet patients' needs due to a lack of focus on the patient as an individual and instead seem to reflect other (corporate) agendas[39]. As Hilary Janks argues, "the analysis of the text increases awareness of the choices the writer has made and every choice foregrounds what was selected and hides what was not selected."[34] Awareness of choices also leads us to question why the writer has made these choices and examine whose interests they serve.

Vocabulary and grammar utilised in the PILs were studied, applying aspects of Fairclough's approach to textual analysis. The textual analysis performed also investigated other aspects of the PILs such as the omissions in the PILs, changes of meaning of key statements in the PILs compared to the PI as well as the layout of the PILs.

As a full textual analysis exceeds the scope of this study, only key findings in the textual analysis are highlighted below:

3.3.1. Vocabulary

The language and words used across all 6 PILs are markedly formal. Whilst the headings used in the PILs, which are mandated by the MCC, are informal (for example, "What X is used for"), the text that appears under these headings are not so. An example of this from the Co Exforge PIL: ***WHAT CO EXFORGE IS USED FOR:*** *CO EXFORGE is used to treat high blood pressure in patients whose blood pressure is adequately controlled on the combination of the three medicines contained in* ***CO EXFORGE,*** *on individual doses.* Similar wording has been used to describe the indications for Exforge and Twynsta, as these medicines contain 2 active ingredients. The manner in which the text is written constructs the patient/ target audience as having good literacy levels as well as a good understanding of the individual active ingredients contained in Co Exforge. It implicates expert knowledge, aimed at the level of a healthcare professional, not a lay person.

Not all sections of the PILs contain words that are formal but the vast majority are. One would argue that as the PIL contains scientific information, it is expected that the text be formal. However, the formality of the text does not serve the interests of patients as it often does not meet the linguistic abilities of a large proportion of the target audience.

The use of highly technical medical terms are also observed in most of the sections of the PILs, without further explanation of these terms. The vocabulary used is thus not ideally suitable for the lay person. Encountering difficult words in the text means that readers are reading at a frustration level and this means that patients are unlikely to complete their reading of the text. If material aimed at the patient is not suitable, the effectiveness and purpose of these materials is ultimately defeated.

The sections of the PILs, Dosage and Directions and Pregnancy and Lactation are the only two sections that contain little or no technical medical terminology. However, upon examining the degree of information agreement for these sections, it can be seen that there are a number of omissions in the PIL. For example, information on the effects of the medicine when taken during pregnancy and lactation is missing in the PILs. Hence, it can be deduced that these sections, had they been reflected completely in the PIL, may have also contained technical terms.

There are indeed situations where certain medical terms cannot be simplified. For example, a clear effort is made to explain information in patient friendly terms in the contraindications section of the Twynsta PIL, however some terms such as “cardiogenic shock” or “porphyria” are not likely to be part of a lay person’s vocabulary. There are also instances where explanation of complex terms by using simple language may actually serve to confuse the patient even further. This can be illustrated by the following statement in the contraindications section of the Cozaar PIL: *Do not take COZAAR if you have hypertrophic obstructive cardiomyopathy, a heart disorder in which the walls of the ventricles (lower heart chambers) thicken (hypertrophy) and become stiff and the thickened muscle blocks the flow of blood out of the heart.* Explanation of this medical condition has significantly lengthened the sentence, which then contributes to a higher readability score. As can be seen from the above statement, even though an explanation is provided for the condition, hypertrophic cardiomyopathy, the vocabulary used in when providing an explanation is also complex. Words such “disorder” could be replaced by a commonly used word such as disease. This is

further illustrated in the following statement from the Co Exforge contraindications section: *If you have previously suffered from the rapid swelling of the skin or mucous membranes of the face (angioedema) while taking this type of medicines, called angiotensin receptor blockers (ARBs). This reaction can also occur without any apparent reason or can be hereditary.* This is an explanation of idiopathic or hereditary angioedema. Terms such “rapid”, “apparent” and “hereditary” are words that could be replaced with simpler, more common words. Explaining a complex medical technical term using difficult words does not create readable texts.

In many cases across all 6 PILs it appears that no attention was paid to ensuring that the vocabulary used was suitable for the lay person. Often, simplification of a technical medical term is quite possible, yet this was overlooked by the pharmaceutical company and the MCC, evaluating the information. As an example, the interactions section of the Exforge PIL contain many complex terms, with no further explanations of their meanings. For example, “complementary medicines” could be described as medicines made mainly from plants. Other complex terms used in this section are “concomitant” and “undesirable interactions”. Across all the PILs, the side effect section contains the largest number of technical terms, where no further explanation is provided. This corresponds with the high Fry’s readability score achieved for the side effects section for all the medicines.

The use of highly technical language in the PIL is indicative of the pharmaceutical companies’ lack of sensitivity to the target audience. The intention of the pharmaceutical company is brought into question. Obscuring information may contribute to less questioning of side effects for example and less queries that the companies will need to field.

There are also instances in the texts where common, everyday words are used, but these words are now used in a medical context, which may confuse patients. An example of this is the side effect of “flushing” listed in the Twynsta PIL. No further explanation for this side effect is provided and a reader with poor literacy may fail to understand how the word “flushing” often associated with the flushing of a toilet, is an actual side effect of the medicine. The side effect of flushing is better explained in the Exforge PIL as “redness and warm feeling of the face and/or the neck”.

Considerable rewording and overwording in the texts was observed. Fairclough states that "overwording shows preoccupation with some aspect of reality, which may indicate it is a focus of ideological struggle[38]." A good example of this phenomenon is seen in the following texts: ***If you take more COZAAR than you should:*** *In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.* This is standardised PIL text as per the PIL guidelines and appears in all PILs. This statement serves to reinforce the severity of an overdose, but ironically the density of the text may undermine the reader who, in the case of an overdose, requires access to clear and immediate information.

3.3.2 Grammar

Modality of the text in the PILs is mainly declarative in nature. This is in line with PIL guidelines that state "An active and direct style should be used, by placing the verb at the beginning of the sentence, for example: '*you should…*' is better than '*it is recommended…*' Hence, nominalisation, the process whereby a verb is converted into a noun, is rarely seen within the texts. This is significant as nominalisation can render the texts even more difficult to read.

However, there are statements in some of the PILs that can be considered ambiguous and may confuse or mislead the reader. The following appears in both the Cozaar and Cozaar Comp PILs: ***Driving and using machinery:*** *Almost all patients can, but you should not perform tasks which may require special attention (e.g. driving a motorcar or operating dangerous machinery) until you know how you tolerate your medicine.* The sentence construction is poor and makes very little sense. It can easily be misconstrued from the text above that it is in fact safe to take Cozaar and Cozaar Comp and still drive and operate machinery. Another example of ambiguity is evident in the Micardis PIL: ***Important information about some of the ingredients of MICARDIS:*** *Sorbitol is not suitable for patients with hereditary fructose intolerance.* It should first be mentioned or reiterated that Micardis contains sorbitol, then the warning should follow. A very concerning misleading sentence is contained in the Twynsta PIL*:* ***If you forget to take TWYNSTA:*** *If you forget to take a dose, do not worry.* A statement like this can lead to non-adherence to treatment and have negative treatment outcomes if the patient misunderstands or fails to read further into

the section, which thereafter states: *Take it as soon as you remember on the same day. If you do not take your tablet on that same day, take your normal dose on the next day. Do not take a double dose to make up for the forgotten individual doses.* Ambiguity in the PILs can be potentially fatal as it can directly impact the safety of the patient. It is imperative that instructions in the PIL should be explicit and clear at all times.

Another common trend seen across the PILs is the incorrect placement of information under headings. An example of this is illustrated in the Cozaar Comp PIL: ***Taking COZAAR COMP with food and drink-*** *COZAAR COMP can be taken with or without food. For convenience and to help you remember, try to take COZAAR COMP at the same time each day.* The second sentence relates to the timing of taking the medicine and does not have anything to do taking the medicine with food or drink. Incorrect placement of information can make it difficult for patients to locate.

Complex sentences are often seen in the PILs, particularly the contraindications, warning and special precautions, interactions and side effects sections. This may contribute to poor comprehension of the texts, particularly in patients with poor literacy skills. Longer complex sentences may contain more than one idea and the meaning behind the sentence may be lost in trying to comprehend all the information put forward. An illustration of this is the following statement from the Co Exforge PIL: *This ingredient may change a person's glucose tolerance (this is used to determine your resistance to glucose and is used to test for diabetes) and raise the levels of cholesterol, triglycerides (fatty acid in the blood), and uric acid (a component in your blood formed from the breakdown of proteins).* These side effects could have been mentioned in 3 separate sentences as opposed to this one sentence.

An observation found in all the PILs was the repetitive use of the word "if" in the contraindications and warnings section of the PIL, where each bullet point starts with "if". Although this practice is recommended in the guidelines, it does affect readability as it makes the text tedious to read.

It is important to consider that even though texts may be considered grammatically correct from a readability point of view, the complex sentences are difficult to understand and may be misunderstood by South Africans whose literacy levels may be below the level of the text.

3.3.3. Omissions

As discussed above in section 3.1, there are a number of omissions in the PILs, in particular the side effect profile. One has to consider how these omissions serve the interests of the pharmaceutical company.

In the case of the Dosage and Directions section, the omissions may be justified. This section in the PIL is critical as it is intended to provide the patient with succinct information regarding the safe and correct use of the medicine. Omission of information such as dosage adjustments is justified as it should be the decision of the attending physician to make dosage adjustments as necessary, depending on the patient's condition and initial response to the medicines.

Obscurity of meaning of the text is sometimes found when explanations are omitted in the PIL. The following statement in the interactions section of the Twynsta PIL serves as an example: *The effect of TWYNSTA may be reduced when you take NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen) or corticosteroids.* The exact meaning of the word "effect" should be clarified, as it is in the PI. This may be misconstrued by patients not as a lack of therapeutic effect, as is intended, but possibly as a lack of adverse "effects".

As mentioned in section 3.1, information pertaining to side effects in the Cozaar and Cozaar Comp PILs are inadequate. The inclusion of the following statement "*Your doctor or pharmacist has a more complete list. Tell your doctor or pharmacist promptly about these or any other unusual symptoms"* can be viewed as patronising and condescending toward the patient. It implies that patients only need access to limited information and signifies the extent of control pharmaceutical companies and healthcare providers have in patient education. This raises the question of access where many South Africans do not have the resources to make multiple trips to healthcare practitioners, or the agency to ask questions.

A perplexing omission in all the PILs studied is around the use of contraceptives in women of childbearing age. ARBs are contraindicated in pregnancy and lactation. As mentioned in the Exforge PI (see Appendix 1.3), use during pregnancy may cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios, hypotension, oliguria and anuria in newborns, have been reported after administration of ACE-inhibitors in the second and third trimester. Teratogenicity has been shown in experimental animals. Furthermore, there have

been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken Exforge. These side effects in pregnant women are life-threatening to the mother and baby. Information in the PIL advising women of child-bearing age to ensure adequate contraception could save lives, yet this information is left out in all the PILs studied. This omission raises concerns pertaining to womens' rights in terms of access to appropriate information.

Another noteworthy omission is the lack of information on supportive treatment in case of overdosage. All the PILs simply advise that help should be sought from a doctor, pharmacist or nearest hospital/ poison control centre. This is based on an assumption that all patients have access to emergency treatment. It does not cater for patients living in rural outlying areas, where medical facilities can be hours away and transport to these facilities are also an issue. Overdosage can be fatal and useful information on supportive treatment in the case of overdosage should be mandatory in all PILs.

The omission information from the PIL is detrimental to the patient and brings the intentions of the pharmaceutical company into question. Were these omissions merely an oversight? Were most side effects intentionally omitted from the PIL so as not to deter patients from using the medicine? Principles of critical discourse analysis would argue that the inclusion or exclusion of information is based on the writer's choices. As there is a trend in omission of certain information across all the PILs, namely overdosage information, it becomes highly unlikely that the omissions were unintentional. Patients' right to complete and accurate information is affected by these omissions and this raises questions about pharmaceutical companies' control of information.

3.3.4 Changes in meaning across PIs and PILs

This section highlights some significant changes of meaning of certain statements in the PI compared to the PIL.

The interactions section in the PI of Cozaar states the following: *In clinical pharmacokinetic trials, no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole and erythromycin.* In the PIL however, the sentence has been adapted inaccurately as: *In general, COZAAR does not*

interact with food or other medicines you may be taking. Similar statements are evident in the PI and PIL of Cozaar Comp. The abovementioned sentence is the first sentence in the interactions section of the PIL. Starting off this section with inaccurate information is extremely dangerous to the patient, particularly because there are a number of medicine interactions that could occur with Cozaar and Cozaar Comp together with other medicines, which are mentioned further on in the PI.

The indications section of Cozaar Comp is also inaccurately reflected in the PIL compared to the PI. The indication as per the PI states: *COZAAR COMP is indicated for the treatment of hypertension in patients established on identical doses of the individual agents,* whereas the indication in the PIL is as follows: *COZAAR COMP is a combination of angiotensin II receptor antagonist (losartan) and a diuretic (hydrochlorothiazide). Losartan and hydrochlorothiazide work together to lower high blood pressure. Your doctor has prescribed* COZAAR COMP *because you have a condition known as hypertension or high blood pressure.* Although the two individual active ingredients of Cozaar Comp are mentioned in the indications section of the PIL, the precise meaning of the indication is changed. This is because the PIL fails to mention that the patient should be already be taking identical doses of the individual ingredients first. A similar distortion of the indication of Exforge is seen in the Exforge PIL. This change in meaning in the PIL is significant as it advocates use in patients who have never been on treatment with the individual components. One could argue that this change in meaning is advantageous to the pharmaceutical company.

There are occurrences in the texts across the Exforge and Co Exforge PILs where a contraindication, which is definitive or absolute, is instead replaced by the words “not recommended”. As defined by the Oxford Dictionary, “recommend” means to advise or suggest (something) as a course of action. An example of this is the following statement in the Exforge PIL “*Treatment with EXFORGE is not recommended during breastfeeding.”* The use of Exforge in lactation is an absolute contraindication, as stated in the PI. Thus, the usage of the words “not recommended” changes the intended meaning from Exforge can absolutely not be used whilst breastfeeding, to it may be used during breastfeeding but it is not advisable.

3.3.5. Layout and Design

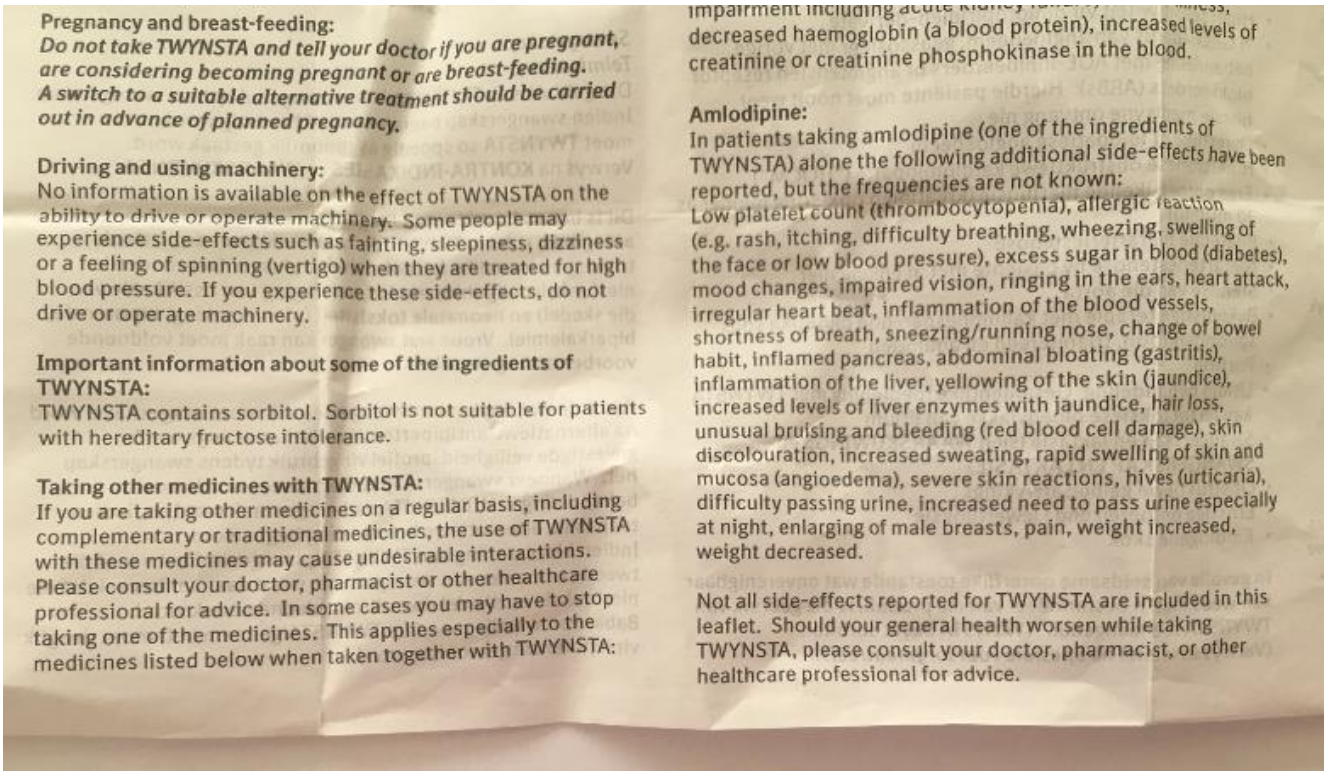
As recommended in the South African PIL guidelines, the text in the PILs analysed are broken down into paragraphs or in bullet points. However, there should be a minimum number of words per paragraph or bullet point which is not demonstrated in the most of the PILs, for example in the Co Exforge, Cozaar and Cozaar Comp PILs. The guidelines also recommend that for simple bullet points per section, a maximum of 9 bullet points is prescribed and where the sentences are complex, there should not be more than 5 bullet points per section. International good practice guidelines on patient leaflet design state that the maximum line length should be between 50-65 characters or 8-11 words as very short lines break up sentences too much; and long lines tend to lose the attention of the reader[2]. The South African PIL guideline however, recommends a maximum of 20 words per sentence, which affects readability.

The typography of the PIL also contributes to its readability. Regulation 10 of Act 101 recommends that the PIL must be made available in a type of minimum legibility, which is defined in the regulations as “printing in 6-point Helvetica, typeface in black ink on white cartridge paper or the equivalent thereof”[16]. All PILs studies comply with this requirement, however, there is no mention in the guidelines regarding the size of the insert paper and the actual design of the PIL, which results in a variety of designs between the PILs studies, where some PILs are more difficult to read due to a smaller size insert paper. Although it has been found that increasing the font size of the PIL too much can make the text appear longer, thereby discouraging readers[2]. Font size as prescribed in the regulation has been found to be too small in other studies[13, 26]. Increasing the text font size to Souvenir size 14 was found to be sufficiently large to readers in a study conducted by L Mansoor and R Dowse[13].

The thin quality of the PIL paper may also lead to poor readability. All the PILs are presented in English on one side and Afrikaans on the reverse side. The paper utilised is quite thin and transparent, and the text on the reverse side is visible through the paper.

Furthermore, the layout of PILs into columns is problematic. Readers could potentially become confused regarding the direction of the text. A case in point is the Twynsta PIL, where the layout of text into columns may lead to confusion in the interactions section or the section titled “Taking other medicines with Twynsta”:

Figure 3: Column representation in Twynsta PIL



Pregnancy and breast-feeding:
Do not take TWYNSTA and tell your doctor if you are pregnant, are considering becoming pregnant or are breast-feeding. A switch to a suitable alternative treatment should be carried out in advance of planned pregnancy.

Driving and using machinery:
No information is available on the effect of TWYNSTA on the ability to drive or operate machinery. Some people may experience side-effects such as fainting, sleepiness, dizziness or a feeling of spinning (vertigo) when they are treated for high blood pressure. If you experience these side-effects, do not drive or operate machinery.

Important information about some of the ingredients of TWYNSTA:
TWYNSTA contains sorbitol. Sorbitol is not suitable for patients with hereditary fructose intolerance.

Taking other medicines with TWYNSTA:
If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of TWYNSTA with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional for advice. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below when taken together with TWYNSTA:

impairment including acute kidney [illegible]
decreased haemoglobin (a blood protein), increased levels of creatinine or creatinine phosphokinase in the blood.

Amlodipine:
In patients taking amlodipine (one of the ingredients of TWYNSTA) alone the following additional side-effects have been reported, but the frequencies are not known:
Low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), excess sugar in blood (diabetes), mood changes, impaired vision, ringing in the ears, heart attack, irregular heart beat, inflammation of the blood vessels, shortness of breath, sneezing/running nose, change of bowel habit, inflamed pancreas, abdominal bloating (gastritis), inflammation of the liver, yellowing of the skin (jaundice), increased levels of liver enzymes with jaundice, hair loss, unusual bruising and bleeding (red blood cell damage), skin discolouration, increased sweating, rapid swelling of skin and mucosa (angioedema), severe skin reactions, hives (urticaria), difficulty passing urine, increased need to pass urine especially at night, enlarging of male breasts, pain, weight increased, weight decreased.

Not all side-effects reported for TWYNSTA are included in this leaflet. Should your general health worsen while taking TWYNSTA, please consult your doctor, pharmacist, or other healthcare professional for advice.

The last sentence indicates that the medicines with which Twynsta interacts is listed below, but that is untrue. It is in fact not below, but above, in the next column. Correct formatting of information when using columns is vital.

The order of information presentation in the South African PIL is not ideal. Important sections for patients should be presented first and within each section, the most important information should appear first. The format of PIL should maintain the reader's attention. However, the layout of the headings in the PIL are dictated by the MCC guidelines, and cannot be changed by the pharmaceutical company. The format and structure of the PIL as prescribed by the MCC is different from that of other international health authorities. A key difference is that the MCC requires the composition section to be presented first whereas this information appears at the end of the PILs in the EU and UK, as prescribed by their respective Health Authorities. The composition section often contains information about ingredients that most patients are completely unfamiliar with and can also not be simplified. The composition section is so

complex in the Cozaar and Cozaar Comp PILs, that a readability score could not be derived. It can be argued that starting the PIL with a complex section such as composition can potentially discourage patients to read further and the patient may already be reading at frustration level from the very first section of the PIL. This undermines the aim of having accessible, patient friendly material. The MCC should thus consider changing the guidelines so that more important information such as indications, contraindications and dosage and directions appear first in the PIL.

On a positive note, the use of blocked warnings, is encouraging. Across the 6 PILs studied, a blocked warning box against the use of the medicines during pregnancy and lactation was illustrated. This highlights the importance of the statement within the block.

Another interesting observation to note in terms of design of the PIL, is the use capitalised text for the tradename of the product throughout all the PILs as well as placing the tradename of the pharmaceutical product in theme position (the word or phrase at the beginning of the sentence). This mainly serves the interests of the pharmaceutical company by entrenching their brand in the mind of the patient.

Studies have found that the use of high contrast print, large font size, prudent use of white space and prominent placement of important information all contribute to improving the readability of the PIL[2].

3.3.6. Summary of Critical Discourse Analysis

The textual analysis of the PILs revealed that the text in the PILs are composite and often unsuitable even to those skilled in the English language, much less to readers who are second language English speakers, as are the majority of the South African population. As highlighted in the vocabulary and grammar sections above, the language and sentence construction used in the in the PILs are complex, despite an effort being made in certain instances to simplify the information. Ambiguous and contradictory information were also found in the PILs. The pharmaceutical companies' choice of language and grammar in a document aimed at the lay person is not always appropriate and raises questions if this is intentional or not, to protect their own interests.

A number of omissions were found across all the PILs studied, where important information was absent. A common trend found was the omission of the use of contraceptives in women of child-bearing age, which is crucial as ARBs are contraindicated in pregnancy and lactation. Another omission discovered across all the PILs studied was the complete lack of information regarding overdosing.

Another important observation from the critical discourse analysis revealed inconsistencies in the meaning of statements in the PIL compared to the true meaning in the PI, such as a change in the meaning of indications of the medicine. The layout and design of the PILs were analysed as well. It was demonstrated that the MCC's guidelines on PIL design is not optimal. PIL design and layout could stand to be improved. Good Information design does not simply improve the presentation of the PIL but it is also instrumental in attracting, motivating and promoting the understanding of the reader.

It can clearly be seen that the theme of patient centricity does not feature largely in these PILs. Most sections contain far too much of medical jargon, thereby making the PIL more acceptable to healthcare professionals than to patients. It may be beneficial to include a thorough linguistic analysis as part of the evaluation of PILs at the health authority.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

The study evaluated the congruency of information in the PIL as compared to the PI of 6 selected antihypertensive drugs in the class of angiotensin receptor blockers. This comparative analysis of the PILs was performed by utilising comprehensive checklists for each PIL. The readability of the PILs was assessed and certain principles of critical discourse analysis were applied for a closer analysis of the texts.

The comparative analysis of information contained in the medicine PILs compared to the corresponding PIs revealed a startling lack of congruency of key information. The degree of information agreement, which refers to the percentage of information present in the PIL compared to the PI, was calculated per section of the PI for each drug included in the study. The highest mean overall information agreement with the PIL was achieved for Micardis at 63.3 % and lowest being for Cozaar Comp at 45.5 %. It can be observed from the results presented that information that contains large amounts of technical medical information such as the interactions and side effects section have low percentages of information agreement with the PIL. One may argue that technical information should not be included in the PIL, however, the guidelines state that the PIL be aligned with the PI and it is unacceptable for information to be omitted from the PIL simply because it is perceived that the patient may not understand it. The selected PILs studied do not contain all the necessary information, thus patients' rights and patient empowerment comes into question.

The Fry's readability analysis confirmed that the PILs in this sample are at a reading level higher than is suitable to the majority of the South African population. As discussed in previous chapters, the prevalence of low literacy rates in South Africa means that material aimed at a large, diverse group of the population should be at a grade 7 level. Although a grade 7 readability level may be considered too high as a recent study has revealed that even South African university students have poor literacy levels and limited vocabulary[40]. Limited vocabulary often leads to poor comprehension of texts. Specialists in health communication in South Africa advise that the readability level should ideally be lowered to the fourth grade[41]. The lowest readability grade level was seen in the Co Exforge and Micardis PILs, which was still too high at grade 11, and the highest grade level observed was 13 for Cozaar. The average number of syllables per 100 words and the average number of sentences per 100

words contribute to determining the readability score. Texts with a higher number of syllables per 100 words may indicate the usage of complex words, thereby increasing the readability grade level of the text. The high grade levels for the PILs raises questions about the construction of the PILs and indicated a need to improve the design, development and evaluation of PILs to cater for the diverse South African population.

The discourse analysis revealed complex vocabulary and sentence construction in the majority of the sections in the PILs analysed. Ambiguity and changes in the actual meaning of phrases were observed in the PILs. The choice of language and presence or absence of certain information in the PILs, used by the pharmaceutical companies puts patients at a disadvantage and raises questions about the integrity of the pharmaceutical companies. Patient safety is ultimately impacted by the poor language usage in the PILs.

To conclude, the creation of a PIL that can be understood by the South African population is complex. An inherent tension exists between creating PILs that effectively convey all necessary information in patient-friendly terms but are structured in a manner that renders them to be at an appropriate readability level. The outcomes of this study are pertinent to pharmaceutical companies, who are the producers of PILs as well as the MCC, that regulate PILs, as they indicate areas for improvement in these texts.

In view of the findings in the study, some practical recommendations include the use of linguistic experts by pharmaceutical companies to aid in producing PILs that are well-written and accessible to the majority of South Africans population. In addition, readability tools can be used by the MCC when evaluating PILs. The MCC could also consider changes in the structure of the PILs to improve layout and accessibility of information. Additionally, the MCC should enforce more stringent criteria when evaluating PILs to ensure compliance with PIL guidelines and completeness of information. Evaluation of PILs by the MCC should include tests on readability and comprehension, and perhaps also consumer testing would be beneficial in ensuring high quality PILs are produced. The MCC will soon be migrating to a new regulatory body called the South African Health Products Regulatory Authority (SAHPRA). This may be the ideal time to implement amendments to guidelines and policy documents relating to PILs, to assist in better regulation of PILs.

The results of this study may suggest that PILs produced currently are ineffective in communicating important safety information and thus adequate patient counselling at physician and pharmacy level is essential.

Further studies conducted in this field of research should include testing patients' understanding of the same PILs used in this study to ascertain if the high readability grade levels observed corresponds with poor comprehension of the PILs. Further research including a larger sample size and a more comprehensive discourse analysis should be carried out. It would also be interesting to conduct an analysis of PILs of the same products utilised in this study but sourced from different countries, like the European PILs, to establish if comparable findings are obtained. Similar studies should also be performed in other therapeutic classes of medicines, particularly OTC, where there is no physician supervising treatment of the medicine to the patient.

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APPENDIX 1
Comparative Tables

Appendix 1.1

Medicine: CO-EXFORGE	
INFORMATION CONTAINED IN THE PI	**PRESENCE OF INFORMATION IN THE PIL** **Yes (Y), No (N)**
Composition *Active ingredient:* 1. CO EXFORGE 5 mg /160 mg /12,5 mg: Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg of amlodipine base), 160 mg of valsartan and 12,5 mg hydrochlorothiazide. 2. Excipients: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous; magnesium stearate; hypromellose, macrogol 4000, talc, titanium dioxide (E171). 3. CO EXFORGE 10 mg /160 mg /12,5 mg: Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 160 mg of valsartan and 12,5 mg hydrochlorothiazide 4. Excipients: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous; magnesium stearate; hypromellose, macrogol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E172). 5. CO EXFORGE 5 mg /160 mg /25 mg: Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg of amlodipine base), 160 mg of valsartan and 25 mg hydrochlorothiazide. 6. Excipients: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous, magnesium stearate, hypromellose, macrogol 4000, talc, titanium dioxide (E171),iron oxide, yellow (E172). 7. CO EXFORGE 10 mg /160 mg /25 mg: Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 160 mg of valsartan and 25 mg hydrochlorothiazide 8. Excipients: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous, magnesium stearate, hypromellose, macrogol 4000, talc, iron oxide, yellow (E172). 9. CO EXFORGE 10 mg /320 mg /25 mg: Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 320 mg of valsartan and 25 mg hydrochlorothiazide 10. Excipients: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous, magnesium stearate, hypromellose, macrogol 4000, talc, iron oxide, yellow (E172).	**WHAT CO EXFORGE CONTAINS:** N Y N Y N Y N Y N Y
Information Agreement with PIL (%)	5/10 = 50%

Indications 1. Treatment of essential hypertension in patients stabilised on individual components given at the same doses. 2. CO EXFORGE is not indicated for the initial therapy of hypertension (see '*Dosage and Directions for Use'*).	**2. WHAT CO EXFORGE IS USED FOR:** Y N
Information Agreement with PIL (%)	1/2 = 50%
Contraindications	**Do not take CO EXFORGE:**
1. Hypersensitivity to amlodipine, valsartan, hydrochlorothiazide and other sulfonamides or to any of the excipients of CO EXFORGE	Y
2. The use of CO EXFORGE during pregnancy and lactation is contraindicated (See *Pregnancy and Lactation*). CO EXFORGE should be discontinued as soon as possible when pregnancy is suspected.	N
3. A history of angioedema related to previous therapy with angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.	
4. Hereditary or idiopathic angioedema	N
5. Severe hepatic impairment.	
6. CO EXFORGE should not be given to patients with Addison's disease.	Y
7. Anuria, severe renal impairment (creatinine clearance less than 30 ml/min).	Y
8. Lithium therapy: Concomitant administration with CO EXFORGE may lead to toxic blood concentrations of lithium. (See *Interactions*).	Y Y
9. Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.	Y
10. Safety and efficacy have not been established in children.	
11. Safety has not been established in porphyria.	Y
12. Hypertrophic obstructive cardiomyopathy (HOCM).	N
13. Bilateral renal artery stenosis.	Y
14. Renal artery stenosis in patients with a single kidney.	Y
15. Aortic stenosis.	Y
16. Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.	Y Y Y
Information Agreement with PIL (%)	13/16 = 81.3%
Warnings **Pregnancy:** 1. When pregnancy is detected, CO EXFORGE should be discontinued as soon as possible. (*See Pregnancy and Lactation)* **Renal Impairment:** 2. Due to the hydrochlorothiazide component, CO EXFORGE is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min), (see '*Contraindications'* and '*Special Precautions'*).	**Take special care with CO EXFORGE:** N N

Hepatic Impairment: 3. Particular caution should be exercised when administering CO EXFORGE to patients with hepatic impairment or biliary obstructive disorders.	Y
4. Because of hydrochlorothiazide, CO EXFORGE is not recommended in patients with severe hepatic impairment. (see '*Contra-indications' and 'Special Precautions'*).	Y
Children: 5. Safety and efficacy of CO EXFORGE in patients aged below 18 years has not been established.	N
Special precautions: ***Sodium- and/or volume depleted patients:*** 6. Excessive hypotension, including orthostatic hypotension was seen in 1,7 % of patients treated with the maximum dose of CO EXFORGE (10/320/25 mg) compared to 1,8 % of valsartan/HCTZ (320/25 mg) patients, 0,4 % of amlodipine/valsartan (10/320 mg) patients, and 0,2 % of HCTZ/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension.	N
7. In patients with an activated renin-angiotensin system, such as volume-and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers.	N
8. This condition should be corrected prior to administration of CO EXFORGE, or the treatment should start under close medical supervision. 9. If excessive hypotension occurs with CO EXFORGE, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of 0,9 % sodium chloride solution. Treatment can be continued once blood pressure has been stabilised.	N
Renal impairment: 10. No dosage adjustment of CO EXFORGE is required for patients with mild to moderate renal impairment.	N
11. Due to the hydrochlorothiazide component, CO EXFORGE is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min), (see *Contra-indications*).	N
Renal artery stenosis: 12. CO EXFORGE should not be used in bilateral renal artery stenosis and renal artery stenosis in patients with a single kidney. (See "Contra-Indications" and "Warnings")	N
Kidney transplantation: 13. There is no experience with the use of CO EXFORGE in patients with recent kidney transplantation.	N
Hepatic impairment: 14. Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolised by the liver. 15. Particular caution should be exercised when administering CO EXFORGE to patients with hepatic impairment or biliary obstructive disorders. Because of hydrochlorothiazide, CO EXFORGE is not recommended in patients with severe hepatic impairment. (see "Contra-indications" and "Warnings").	N Y
Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: 16. Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy. (See Contra-Indications)	N

Serum electrolyte changes:	
Hydrochlorothiazide:	
17. Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) could lead to hyperkalaemia and should be used with caution.	N
18. Hypokalaemia has been reported under treatment with thiazide diuretics including hydrochlorothiazide.	
19. Frequent monitoring of potassium is recommended. (See Contra-Indications)	N
20. Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloroaemic alkalosis.	Y N
21. Thiazides, including hydrochlorothiazide increase the urinary excretion of magnesium, which may result in hypomagnesaemia.	
22. As for any patient receiving diuretic therapy, periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals.	N
Amlodipine -Valsartan - Hydrochlorothiazide:	N
23. In the controlled trial of CO EXFORGE in moderate to severe hypertensive patients [54], the incidence of hypokalaemia (serum potassium <3,5 mmol/L) at any time post-baseline with the maximum dose of CO EXFORGE (10/320/25 mg) was 9,9 % compared to 24,5 % with HCTZ/amlodipine (25/10 mg), 6,6 % with valsartan/HCTZ (320/25 mg), and 2,7 % with amlodipine/valsartan (10/320 mg).	N
24. One patient (0,2 %) discontinued therapy due to an adverse event of hypokalaemia in each of the CO EXFORGE and HCTZ/amlodipine groups.	N
25. The incidence of hyperkalaemia (serum potassium > 5,7 mmol/L) was 0,4 % with CO EXFORGE compared to 0,2 - 0,7 % with the dual therapies.	N
26. In the controlled trial of CO EXFORGE, the opposite effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant.	N
27. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.	Y
Systemic lupus erythematosus:	
28. Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.	Y
Other metabolic disturbances:	
29. Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides, and uric acid.	Y
Effects on ability to drive and use machines:	
30. No studies on the effects on the ability to drive and use machines have been performed.	N
31. When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.	Y
Information Agreement with PIL (%)	8/31 = 25.8%
Interactions **Amlodipine:**	**Taking other medicines with CO EXFORGE**

1. In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, aluminium hydroxide gel, magnesium hydroxide and simethicone, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic medicines.	N
Valsartan:	N
2. In monotherapy with valsartan, no medicine interactions of clinical significance have been found with the following medicines: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.	
3. Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.	Y
Hydrochlorothiazide :	Y
4. Lithium: Increases in serum lithium concentrations and toxicity may occur during concurrent use of CO EXFORGE. (*See Contraindications*)	Y
5. Non-depolarising muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of non-depolarising muscle relaxants:	Y
6. Non-steroidal anti-inflammatory drugs: Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of CO EXFORGE. Concurrent hypovolaemia may induce acute renal failure.	Y
7. Medicinal products affecting potassium: The hypokalaemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives.	Y
8. Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digoxin-induced cardiac dysrhythmias.	Y
9. Antidiabetic medicinal products: It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents.	Y
10. Anticholinergic agents: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.	Y
11. Methyldopa: There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.	Y
12. Cholestyramine: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine.	Y
13. Vitamin D and calcium salts: Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.	Y
14. Ciclosporin: Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.	Y
15. Carbamazepine: Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.	Y
16. Other interactions: Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol, may increase the risk of adverse effects caused by amantadine, may enhance the hyperglycaemic effect of diazoxide, and may reduce the renal excretion of cytotoxic medicines (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.	N
Information Agreement with PIL (%)	13/16

	= 81.3%
Pregnancy and Lactation **Pregnancy:** 1. CO EXFORGE is contraindicated in pregnancy as teratogenicity has been shown in experimental animals. 2. Medicines affecting the renin-angiotensin system, such as CO EXFORGE, can cause foetal and neonatal morbidity and mortality when administered to pregnant women. 3. When pregnancy is detected, CO EXFORGE should be discontinued as soon as possible. 4. Women of childbearing age should use effective contraception. **Lactation:** 5. It is not known whether valsartan and/or amlodipine are excreted in human milk. 6. Valsartan was excreted in the milk of lactating rats. 7. Hydrochlorothiazide is excreted into breast milk. 8. CO EXFORGE is contra-indicated in women who are breast-feeding	**Pregnancy and breast-feeding:** Y Y N N N N N Y
Information Agreement with PIL (%)	3/8 = 37.5%
Dosage and Directions for Use 1. The recommended dose is one tablet per day (the 5 strengths are listed under *Composition*). 2. If a tablet show signs of cracking the tablet should not be taken. 3. Patients stabilised with valsartan, amlodipine and HCTZ from separate tablets may be switched to CO EXFORGE containing the same component doses. 4. The maximum antihypertensive effect of CO EXFORGE is reached within two weeks after a change in dose. 5. The maximum recommended dose of CO EXFORGE is 10/320/25 mg. 6. CO EXFORGE can be taken with or without food. 7. It is recommended to take CO EXFORGE with some water. **In elderly:** 8.No adjustment of the initial dose is required for elderly patients (see *Pharmacokinetic properties*). **Children and adolescents (below 18 years):** 9. CO EXFORGE is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy. **Renal and hepatic impairment:** 10. No dosage adjustment is required for patients with mild to moderate renal impairment but caution should be exercised when administering CO EXFORGE to patients with hepatic impairment or biliary obstructive disorders (see *Side effects* and *Special precautions*). 11. Due to the hydrochlorothiazide component, CO EXFORGE is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in patients with severe hepatic impairment (see *Contra-indications* and *Pharmacokinetic properties*).	**HOW TO TAKE CO EXFORGE**: Y Y N N N Y Y Y N N N

Information Agreement with PIL (%)	5/11 = 45.5%
Side Effects and Special Precautions **Side-effects:**	**POSSIBLE SIDE EFFECTS:**
1. The presentation of the safety profile of CO EXFORGE is based on the experience with CO EXFORGE, and the individual components.	N
Information on CO EXFORGE :	
2. The safety of CO EXFORGE has been evaluated at its maximum dose of 10/320/25 mg for safety in one controlled clinical study with 2 271 patients, 582 of whom received valsartan in combination with amlodipine and HCTZ.	N
3. There were no known adverse reactions which occurred specifically with CO EXFORGE in addition to those known to be associated with the individual components.	N
Information on individual components:	
4. Adverse reactions previously reported with one of the individual components may occur with CO EXFORGE even if not observed in the pivotal clinical trial.	N
5. Adverse drug reactions observed are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.	N
Amlodipine:	
6. Adverse experiences reported with amlodipine monotherapy, irrespective of their causal association with the study medicine were as follows:	N
Blood and lymphatic system disorders:	
7. Very rare: Thrombocytopenia, leucocytopenia	Y
Immune system disorders:	
8. Very rare: Allergic reactions; Angioedema	Y
Metabolism and nutrition disorders:	
9. Very rare: Hyperglycaemia	Y
Psychiatric disorders:	
10.Uncommon: Insomnia, mood changes including anxiety	N
Nervous system disorders:	
11. Common: Headache, somnolence, dizziness	Y
12. Uncommon: Tremor, hypoesthesia, dysgeusia, paraesthesia, syncope	Y
13. Very rare: Peripheral neuropathy, hypertonia	Y
Eye disorders:	
14. Uncommon: Visual impairment, diplopia	Y
Ear and labyrinth disorders:	
15. Uncommon: Tinnitus	Y
Cardiac disorders:	

16. Common: Palpitations	Y
17. Very rare: Dysrhythmia, bradycardia, atrial fibrillation, ventricular tachycardia, myocardial infarction	Y
Vascular disorders:	
18. Common: Flushing	Y
19. Uncommon: Hypotension	Y
20. Very rare: Vasculitis	Y
Respiratory, thoracic and mediastinal disorders:	
21. Uncommon: Dyspnoea, rhinitis	Y
22. Very rare: Cough	Y
Gastrointestinal disorders:	
23. Very common: Vomiting	Y
24. Common: Abdominal pain, nausea	Y
25. Uncommon: Dyspepsia, dry mouth, constipation, diarrhoea	Y
26. Very rare: Pancreatitis, gastritis, gingival hyperplasia	Y
Hepatobiliary disorders:	
27. Very rare: Hepatitis, jaundice	Y
Skin and subcutaneous tissue disorders	
28. Uncommon: Alopecia, hyperhidrosis, pruritus, rash, purpura, skin discoloration, photosensitivity	N
29. Very rare: Urticaria, erythema multiforme, Stevens-Johnson syndrome	Y
Musculoskeletal and connective tissue disorders:	
30. Uncommon: Back pain, muscle spasms, myalgia, arthralgia	Y
Renal and urinary disorders:	
31. Uncommon: Micturition disorder, nocturia, pollakiuria	Y
Reproductive system and breast disorders:	
32. Uncommon: Gynecomastia, erectile dysfunction	Y
General disorders and administration site conditions:	
33. Common: Oedema, fatigue	Y
34. Uncommon: Asthenia, pain, malaise, chest pain	Y
Investigations:	
35. Uncommon: Weight decreased, weight increased	N
36. Very rare: Hepatic enzyme increased *(mostly consistent with cholestasis)*	N
Valsartan:	
37. Adverse Drug Reactions (ADRs) reported in the hypertension indication from clinical studies and laboratory findings are listed below according to system organ class.	
For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.	N
Infections and Infestations:	
38. Frequency not known: viral infections, upper respiratory tract infection, sinusitis, pharyngitis, rhinitis	N

Blood and lymphatic system disorders:	
39. Frequency not known: Decrease in haemoglobin, Decrease in haematocrit, Neutropenia	Y
Immune system disorders:	
40. Frequency not known: Hypersensitivity including serum sickness , angioedema	Y
Psychiatric disorders:	
41. Frequency not known: Insomnia, decrease libido,	N
Ear and labyrinth disorders:	
42. Less frequent: Vertigo	Y
Respiratory, thoracic and mediastinal disorders:	
43. Less frequent: Cough	Y
Gastrointestinal disorders:	
44. Less frequent: Abdominal pain	Y
Skin and subcutaneous tissue disorders:	
45. Frequency not known: Rash, Pruritus	Y
Renal and urinary disorders:	
46. Frequency not known: Elevation of serum creatinine, increased blood urea	N
General disorders and administration site conditions:	
47. Less frequent: Fatigue	Y
Post Marketing data:	
Blood and lymphatic system disorders:	
48. Frequency not known: Thrombocytopenia	Y
Immune system disorders:	
49. Frequency not known: Angioedema	Y
Metabolism and nutrition disorders:	
50. Frequency not known: Increase of serum potassium	N
Vascular disorders:	
51. Frequency not known: Vasculitis	Y
Hepato-biliary disorders:	
52. Frequency not known: Elevation of liver function values including serum bilirubin	N
Musculoskeletal and connective tissue disorders:	
53. Frequency not known: Myalgia	Y
Renal and urinary disorders:	
54. Frequency not known: Renal failure and impairment, Elevation of serum creatinine	N
Hydrochlorothiazide:	
55. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:	N
Blood and lymphatic system disorders:	

56. Less frequent: thrombocytopenia sometimes with purpura, leucopenia, agranulocytosis, bone marrow failure, haemolytic anaemia, aplastic anaemia	N
Immune system disorders:	
57. Less frequent: hypersensitivity reactions – respiratory distress including pneumonitis and pulmonary oedema.	Y
Metabolism and nutrition disorders:	
58. Frequent: (mainly at higher doses) hypokalaemia, increased blood lipids, hyponatremia, hypomagnesaemia, hyperuricaemia.	N
59. Less frequent: hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state, hypochloraemic alkalosis.	N
Nervous system disorders:	
60. Less frequent: Headache, dizziness, sleep disorders, depression, paraesthesia.	N
Eye disorders:	
61. Less frequent: Visual impairment particularly in the first few weeks of treatment. Acute angle-closure glaucoma.	Y
Cardiac disorders:	
62. Less frequent: dysrhythmias.	Y
Vascular disorders:	
63. Frequent: orthostatic hypotension, which may be aggravated by alcohol, anesthetics or sedatives.	Y
Gastrointestinal disorders:	
64. Frequent: decreased appetite, mild nausea, vomiting.	Y
65. Less frequent: abdominal discomfort, constipation, diarrhoea, pancreatitis.	Y
Hepatobiliary disorders:	
66. Less frequent: cholestasis or jaundice.	Y
Skin and subcutaneous tissue disorders:	
67. Frequent: urticaria and other forms of rash.	Y
68. Less frequent: photosensitivity reaction, necrotizing vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, erythema multiforme	Y
Musculoskeletal and connective tissue disorders:	
69. Less frequent: muscle spasms	Y
Renal and urinary disorders:	
70. Less frequent: acute renal failure.	Y
Reproductive system and breast disorders:	
71. Frequent: impotence.	Y
General disorders and administration site conditions:	
72. Less frequent: pyrexia, asthenia	Y
Information Agreement with PIL (%)	50/72 = 69.4%
Known Symptoms of Overdosage and Particulars of its Treatment	**If you take more Co Exforge than you should:**

1. There is no experience of overdose with CO EXFORGE. 2. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. 3. Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. 4. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. 5. If the ingestion is recent, induction of vomiting or gastric lavage may be considered. 6. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. 7. Clinically significant hypotension due to CO EXFORGE overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. 8. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. 9. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. 10. Both valsartan and amlodipine are unlikely to be removed by haemodialysis whereas clearance of HCTZ will be achieved by dialysis.	N N N N N N N N N N
Information Agreement with PIL (%)	0/10 = 0

Appendix 1.2

Medicine: COZAAR	
INFORMATION CONTAINED IN THE PI	**PRESENCE OF INFORMATION IN THE PIL** **Yes (Y), No (N)**
Composition 1. Each tablet of COZAAR contains 50 mg losartan potassium 2. Each tablet of COZAAR 100 contains 100 mg losartan potassium 3. Contains lactose	**WHAT COZAAR CONTAINS** Y Y Y
Information Agreement with PIL (%)	3/3= 100 %
Indications HYPERTENSION 1. COZAAR is indicated for the treatment of hypertension. 2. RENAL PROTECTION IN TYPE 2 DIABETIC PATIENTS WITH HYPERTENSION AND PROTEINURIA	**WHAT COZAAR IS USED FOR** Y Y
Information Agreement with PIL (%)	2/2= 100 %
Contraindications COZAAR is contra-indicated in patients 1. who are hypersensitive to any component of this product. 2. with a history of angiooedema related to ACE inhibitors or angiotensin receptor antagonists such as COZAAR. 3. COZAAR is not recommended for patients with severe renal impairment or for patients with hepatic impairment. 4. Aortic stenosis, left ventricular outflow track obstruction. 5. Hypertrophic obstructive cardiomyopathy 6. Agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with COZAAR; these changes in renal function may be reversible upon discontinuation of therapy. 7. Bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney	**Do not take COZAAR:** Y Y Y Y Y Y Y

8. Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride 9. Pregnancy and lactation (see **PREGNANCY AND LACTATION**) Paediatric Use 10. Safety and effectiveness in children have not been established.	Y Y N
Information Agreement with PIL (%)	9/10= 90 %
Warnings 1. Should a woman become pregnant while receiving COZAAR, the treatment must be stopped promptly and changed to a different medicine (see PREGNANCY AND LACTATION). 2. If a woman is contemplating pregnancy, a different class of medicine should be used (see PREGNANCY AND LACTATION). 3. Serum potassium levels should be monitored regularly**.**	**Take special care with COZAAR:** N N N
Information Agreement with PIL (%)	0/3= 0 %
Interactions 1. In clinical pharmacokinetic trials, no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole and erythromycin. 2. Rifampin and fluconazol have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated. 3. Concomitant use of medicines that block angiotensin II or its effects and potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium, may lead to increases in serum potassium. 4. As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. 5. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co- administered with angiotensin II receptor antagonists.	**Taking other medicines with COZAAR** N N Y Y N

6. Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. 7. Therefore, the antihypertensive effect of angiotensin II receptor antagonists may be attenuated by NSAIDs including selective COX-2 inhibitors. 8. In some patients with compromised renal function who are being treated with non-steroidal anti- inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.	Y N N
Information Agreement with PIL (%)	3/8= 37.5 %
Pregnancy and Lactation **Pregnancy** 1. When pregnancy is detected, COZAAR should be discontinued as soon as possible. 2. Not to be used in pregnancy as teratogenicity has been shown in experimental animals. 3. Women of childbearing age should ensure adequate contraception. **Breast feeding mothers** 4. It is not known whether losartan is excreted in human milk. 5. Safety of breast feeding in mothers taking COZAAR has not been established. 6. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. (see CONTRA-INDICATIONS)	**Pregnancy and breast-feeding:** Y Y N N N N
Information Agreement with PIL (%)	2/6= 33.3 %

Dosage and Directions for Use 1. COZAAR may be administered with or without food. 2. COZAAR may be administered with other antihypertensive agents. <u>HYPERTENSION</u> 3. The usual starting and maintenance dose is 50 mg once daily for most patients. 4 . The maximal antihypertensive effect is attained 3 to 6 weeks after initiation of therapy. 5. The dose may be increased to 100 mg once daily. 6. For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see **SPECIAL PRECAUTIONS**). 7. No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis. 8 . A lower dose should be considered for patients with a history of hepatic impairment (see **SPECIAL PRECAUTIONS**). <u>RENAL PROTECTION IN TYPE 2 DIABETIC PATIENTS WITH HYPERTENSION AND PROTEINURIA</u> 9. The usual starting dose is 50 mg once daily. 10. The dose may be increased to 100 mg once daily based on blood pressure response. 11. COZAAR may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).	**HOW TO TAKE COZAAR** Y N Y N N N N Y Y N .
Information Agreement with PIL (%)	4/11= 36.4 %

Side Effects and Special Precautions SIDE EFFECTS	**SIDE EFFECTS** **What undesirable effects may COZAAR have?**
1. In controlled clinical trials for essential hypertension, the following adverse experiences were reported, regardless of drug relationship, and are shown in decreasing order of frequency within body system.	N
[Very common (more than or equal to 1/10), Common (more than or equal to 1/100, less than 1/10), Uncommon (more than or equal to 1/1,000, less than 1/100) and Rare (more than or equal to 1/10,000, less than 1/1,000)]	
2. Infections and infestations: Common: upper respiratory infection	N
3. Psychiatric disorders: Common: insomnia	N
4. Nervous system disorders: Very common: headache Common: dizziness, vertigo	Y
5. Cardiac disorders: Common: palpitation, tachycardia	N
6. Vascular disorders: Uncommon: orthostatic hypotension	N
7. Respiratory, thoracic and mediastinal disorders: Common: cough, pharyngitis, nasal congestion, sinus disorder	N
8. Gastro-intestinal disorders: Common: diarrhoea, nausea, abdominal pain, dyspepsia	N
9. Skin and subcutaneous tissue disorders: Uncommon: rash	N
10. Musculoskeletal, connective tissue and bone disorders: Common: back pain, muscle cramps	Y
11. General disorders and administration site conditions: Common: asthenia/fatigue, oedema/swelling, chest pain	N
Investigations:	N

12. Common: hyperkalaemia, elevations of ALT	Y
13. The following adverse reactions have been reported in post-marketing experience; they are derived from spontaneous reports for which precise incidences cannot be determined, therefore the frequency is unknown:	N
14. Blood and lymphatic system disorders: Anaemia	N
Immune system disorders: 15. Anaphylactic reactions, angio-oedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angio-oedema with ACE inhibitors and angiotensin receptor blockers.	Y
16. Nervous system disorders: Migraine, dysgeusia.	Y
Vascular disorders: 17. Vasculitis, including Henoch-Schönlein purpura	N
18. Respiratory, thoracic and mediastinal disorders: Cough	N
19. Hepato-biliary disorders: Hepatitis	N
20. Skin and subcutaneous tissue disorders: Urticaria, pruritis, erythroderma	Y
21. Musculoskeletal, connective tissue and bone disorders: Myalgia, arthralgia.	N
Investigations:	
22. Liver function abnormalities	N
23. Haematological disorders: Thrombocytopenia (reported rarely)	N
24. Gastro-intestinal: Vomiting	Y

SPECIAL PRECAUTIONS 25. Hypersensitivity: Angio-oedema (see SIDE EFFECTS)	
Hypotension and Electrolyte/Fluid Imbalance 26. In patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND DIRECTIONS FOR USE).	Y N
27. Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalaemia was higher in the group treated with COZAAR as compared to the placebo group; however, few patients discontinued therapy due to hyperkalaemia (see SIDE EFFECTS).	Y
28. Liver Function Impairment Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a dose of 25 mg should be considered for patients with a history of hepatic impairment (see DOSAGE AND DIRECTIONS FOR USE).	Y
29. Renal Function Impairment When impaired renal function is present, changes in renal function as a consequence of inhibiting the renin-angiotensin system, including renal failure, have been reported in susceptible individuals; in some patients these changes in renal function may be reversible upon discontinuation of therapy.	Y
30.In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (less frequently) with acute renal failure and/or death. Similar outcomes have been reported with COZAAR.	N
31. Agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery	

stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with COZAAR; these changes in renal function may be reversible upon discontinuation of therapy. Porphyria 32. Limited information is available regarding the effect of antihypertensive medication in patients with porphyria. 33. Safety of losartan in patients with porphyria has not been fully established. Use in the Elderly 34. In clinical studies there was no age-related difference in efficacy or safety profile of losartan. Effects on Ability to Drive and Use Machines 35. There are no data to suggest that COZAAR affects the ability to drive and use machines.	N Y N N N
Information Agreement with PIL (%)	12/35= 34.3 %
Known Symptoms of Overdosage and Particulars of its Treatment 1. Limited data are available in regard to overdosage in humans. 2 . The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. 3 . If symptomatic hypotension should occur, supportive treatment should be instituted. 4. Neither losartan nor the active metabolite can be removed by haemodialysis.	**If you take more COZAAR than you should:** N N N N
Information Agreement with PIL (%)	0/4= 0 %

Appendix 1.3

Medicine: EXFORGE	
INFORMATION CONTAINED IN THE PI	**PRESENCE OF INFORMATION IN THE PIL** **Yes (Y), No (N)**
Composition *Active ingredient:* 1. Exforge 5/80 mg: Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg amlodipine base) and 80 mg valsartan 2. Exforge 5/160 mg: Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg amlodipine base) and 160 mg valsartan 3. Exforge 10/160 mg: Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg amlodipine base) and 160 mg valsartan 4. Exforge 5/320 mg: Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg amlodipine base) and 320 mg valsartan 5. Exforge 10/320 mg: Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg amlodipine base) and 320 mg valsartan List of excipients: 6. Exforge 5/80 mg: Microcrystalline cellulose; crospovidone; colloidal silicon dioxide, anhydrous; magnesium stearate; hypromellose; polyethylene glycol 4000; talc; titanium dioxide (E171); iron oxide, yellow (E172) 7. Exforge 5/160 mg: Microcrystalline cellulose; crospovidone; colloidal silicon dioxide, anhydrous; magnesium stearate; hypromellose; polyethylene glycol 4000; talc; titanium dioxide (E171); iron oxide, yellow (E172) 8. Exforge 10/160 mg: Microcrystalline cellulose; crospovidone; colloidal silicon dioxide, anhydrous, magnesium stearate; hypromellose; polyethylene glycol 4000; talc; titanium dioxide (E171); iron oxide, yellow (E172); iron oxide, red (E172) 9. Exforge 5/320 mg: Microcrystalline cellulose; sodium starch glycolate, crospovidone; colloidal silicon dioxide, anhydrous; magnesium stearate; hypromellose, polyethylene glycol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E172) 10. Exforge 10/320 mg: Microcrystalline cellulose; sodium starch glycolate, crospovidone; colloidal silicon dioxide, anhydrous; magnesium stearate; hypromellose, polyethylene glycol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E172)	**WHAT EXFORGE CONTAINS** Y Y Y Y Y Y Y Y Y

Information Agreement with PIL (%)	=0/10 =100 %
Indications 1. Treatment of mild to moderate essential hypertension in patients whose blood pressure is normalized with the individual components in the same doses as the proposed fixed dose combination of Exforge.	**What Exforge Is Used For** Y
Information Agreement with PIL (%)	1/1 =100 %
Contraindications 1. Sensitivity to any of the components of Exforge. 2. A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines. 3. Hereditary or idiopathic angioedema 4. Hypertrophic obstructive cardiomyopathy (HOCM) 5. Aortic stenosis 6. Severe renal function impairment (creatinine clearance less than 30 ml/min) 7. Bilateral renal artery stenosis. 8. Renal artery stenosis in patients with a single kidney 9. Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride. 10. Porphyria. 11. Lithium therapy: Concomitant administration with Exforge may lead to toxic blood concentrations of lithium. 12. Pregnancy and lactation (see Pregnancy and lactation).	**Before You Take Exforge** **Do Not Take Exforge:** Y N N Y Y Y Y Y Y N Y Y
Information Agreement with PIL (%)	9/12 = 75%
Warnings *Renal Impairment:*	**Take special care with EXFORGE:**

1. Amlodipine is extensively metabolised to inactive metabolites with 10 % excreted unchanged in the urine. Changes in amlodipine plasma concentrations are not correlated with mild renal impairment. Exforge may be used in such patients at normal doses. In patients with severe renal impairment, Exforge containing reduced amlodipine dosages (5 mg) may need to be administered in these patients. Amlodipine is not dialysable. *Hepatic Impairment:* 2. Amlodipine half-life is prolonged in patients with impaired liver function. Exforge containing lower amlodipine dosages (5 mg) should therefore be administered in these patients. *Children:* 3. Safety and effectiveness of Exforge in children has not been established.	Y Y Y
Information Agreement with PIL (%)	3/3 =100%
Interactions **Amlodipine** 1. In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, *digoxin, warfarin, atorvastatin, sildenafil, Maalox® (Aluminium hydroxide gel, Magnesium hydroxide and Simeticone), cimetidine*, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic medicines. 2. Studies have indicated that the co-administration of monotherapy amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of amlodipine. *3. In vitro* data from studies with human plasma indicate that monotherapy amlodipine has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin). In healthy male volunteers, the co-administration of monotherapy amlodipine does not significantly alter the effect of warfarin on prothrombin response time. 4. Pharmacokinetics studies with cyclosporin have demonstrated that monotherapy amlodipine does not significantly alter the pharmacokinetics of cyclosporin. **Valsartan**	**Taking other medicines with EXFORGE:** N N N N

5. In monotherapy with valsartan, no interactions of clinical significance have been found with the following medicines: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. 6. Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels (see Contra-indications).	N Y
Information Agreement with PIL (%)	1/6 =16.7%
Pregnancy and Lactation 1. ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. 2. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of ACE-inhibitors in the second and third trimester. 3. Safety in pregnancy and lactation has not been established 4. Exforge acts directly on the renin-angiotensin system therefore a risk to the foetus cannot be excluded. 5. When pregnancy is detected during therapy, Exforge must be discontinued as soon as possible. 6. Exforge must not be used during pregnancy as teratogenicity has been shown with valsartan in experimental animals (see Contra-indications). 7. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan. Lactation: 8. It is not known whether valsartan and/or amlodipine are excreted in human milk. 9. Valsartan was excreted in the milk of lactating rats. 10. Exforge is contra-indicated for women who are breast-feeding (see Contra-indications).	Pregnancy and Breastfeeding N Y N N N Y N N N Y
Information Agreement with PIL (%)	3/10 =30%

Dosage and Directions for Use 1. Patients receiving valsartan and amlodipine from separate tablets may be switched to Exforge containing the same component doses. **2.** The recommended dose is one tablet per day (the 5 strengths are listed under Composition). 3. It is recommended to take Exforge with some water. 4. In Elderly: Normal dosage regimens are recommended 5. Children and adolescents: Exforge is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy (see Warnings). 6. Renal impairment: No dosage adjustment is required for patients with mild to moderate renal impairment. In patients with severe renal impairment dosages may need to be reduced (see Warnings). 7. Hepatic impairment: Caution should be exercised when administering Exforge to patients with hepatic impairment or biliary obstructive disorders (see Side-effects and Special Precautions).	**How To Take Exforge** N Y Y N N N N
Information Agreement with PIL (%)	2/7 =28.6%
Side Effects and Special Precautions **Side-effects:** 1. The safety of Exforge has been evaluated in five controlled clinical studies with 5 175 patients, 2 613 of whom received valsartan in combination with amlodipine at variable dosage combinations. 2. Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000) very rare (< 1/10 000), including isolated reports. 3. **Infections and infestations**- Common: Nasopharyngitis, influenza **4. Immune system disorders-** Rare: Hypersensitivity **5. Eye disorders-** Rare Visual disturbance	**Possible Side Effects** N N Y Y Y

6. Psychiatric disorders Rare: Anxiety	Y
7. Nervous system disorders Common: Headache Uncommon: Dizziness, somnolence, dizziness postural, paraesthesia	Y
8. Ear and labyrinth disorders Uncommon: Vertigo Rare: Tinnitus	Y
9. Cardiac disorders Uncommon: Tachycardia, palpitations Rare: Syncope	Y
10. Vascular disorders Uncommon: Orthostatic hypotension Rare: Hypotension	Y
11. Respiratory, thoracic and mediastinal disorders Uncommon: Cough, pharyngolaryngeal pain	Y
12. Gastrointestinal disorders Uncommon: Diarrhoea, nausea, vomiting, abdominal pain, constipation, dry mouth	Y
13. Skin and subcutaneous tissue disorders Uncommon: Rash, erythema Rare: Hyperhidrosis, exanthema, pruritus	Y
14. Musculoskeletal and connective tissue disorders Uncommon: Joint swelling, back pain, arthralgia Rare: Muscle spasm, sensation of heaviness	Y
15. Renal and urinary disorders Rare: Pollakiuria, polyuria	Y
16. Reproductive system and breast disorders Rare: Erectile dysfunction	N
17. General disorders and administration site conditions Common: Oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flushes	Y
18. Additional information on the combination	

In double-blind, active- or placebo-controlled completed clinical trials, the incidence of peripheral oedema was statistically lower in patients treated with the combination (5,8 %) than in patients treated with amlodipine monotherapy (9 %).	Y
19. Additional information on individual components Adverse reactions previously reported with one of the individual components may occur with Exforge even if not observed in clinical trials.	N
Amlodipine	
20. Blood and lymphatic system disorders: Uncommon: Leucopenia, thrombocytopenia,	N
21. Metabolism and nutrition disorders: Uncommon: Hyperglycaemia	N
22. Eye disorders: Uncommon: Visual Disturbances	Y
23. Nervous system disorders: Common:Headache, somnolence, Uncommon: dizziness Peripheral neuropathy	Y
24. Cardiac disorders: Common: Palpitations Uncommon:Syncope	Y
25. Hepato-biliary disorders: Uncommon: Pancreatitis, hepatitis	Y
26. Vascular disorders: Uncommon: Angioedema, vasculitis	Y
27. Respiratory, thoracic and mediastinal disorders: Uncommon: Dyspnoea, rhinitis	Y
28. Gastrointestinal disorders: Common: Nausea, vomiting, abdominal pain Uncommon: Altered bowel habits, dyspepsia, gastritis, gingival hyperplasia, dry mouth,	Y
29. Skin and subcutaneous tissue disorders: Uncommon: Alopecia, increased sweating, pruritus, rash, erythema multiforme	Y
30. Musculoskeletal and connective tissue disorders: Uncommon: Myalgia, arthralgia, back pain, muscle cramps	Y
31. Renal and urinary disorders:	

Uncommon: Increased urinary frequency	Y
32. General disorders and administration site conditions:	
Common: Oedema, fatigue, flushing	Y
Uncommon: Malaise, mood changes, depression, asthenia	
33. Reproductive system and breast disorders	
Uncommon: Gynaecomastia, impotence	Y
34. In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.	N
Valsartan	
35. Infections and infestations:	
Common: Viral infections	N
Uncommon: Upper respiratory tract infection, pharyngitis, sinusitis	
Very rare: Rhinitis	
36. Blood and lymphatic system disorders:	
Common: Neutropenia	Y
Very rare: Thrombocytopenia	
37. Immune system disorders:	
Very rare: Hypersensitivity including serum sickness	Y
38. Metabolism and nutrition disorders:	
Uncommon: Hyperkalaemia	Y
39. Psychiatric disorders:	
Uncommon: Insomnia, libido decrease	Y
40. Nervous system disorders:	
Common: Postural dizziness	
Uncommon: Syncope	Y
Rare: Dizziness	
Very rare: Headache	
41. Ear and labyrinth disorders:	
Uncommon: Vertigo	Y
42. Cardiac disorders:	
Uncommon: Cardiac failure	Y
43. Vascular disorders:	

Common: Orthostatic hypotension Uncommon: Hypotension Very rare: Vasculitis	Y
44. Respiratory, thoracic and mediastinal disorders: Uncommon: Cough	Y
45. Gastrointestinal disorders: Uncommon: Diarrhoea, abdominal pain Very rare: Nausea	Y
46. Skin and subcutaneous tissue disorders: Very rare: Angioneurotic oedema, rash, pruritus	Y
47. Musculoskeletal and connective tissue disorders: Uncommon: Back pain Very rare: Arthralgia, myalgia	Y
48. Renal and urinary disorders: Very rare: Renal impairment, acute renal failure, renal insufficiency	Y
49. General disorders and administration site conditions: Uncommon: Fatigue, asthenia, oedema	Y
Special precautions:	
50. Sodium- and/or volume depleted patients: Excessive hypotension was seen in 0,4 % of patients with uncomplicated hypertension treated with Exforge in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Exforge or close medical supervision at the start of treatment is recommended. If hypotension occurs with Exforge, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.	Y
51. Hyperkalaemia: Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium (see Contra-indications).	N

52. **Renal artery stenosis:** (See Contra-indications)	N
53. **Hepatic impairment**: Particular caution should be exercised when administering Exforge to patients with hepatic impairment or biliary obstructive disorders. Exforge containing lower (5 mg) initial dose of amlodipine should be administered in these patients.	Y
54. **Renal impairment:** No dosage adjustment of Exforge is required for patients with mild to moderate renal impairment. However, no data is available for severe cases (creatinine clearance <10 ml/min.) and caution is therefore advised.	Y
55. **Effects on ability to drive and use machines:** No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.	Y
Information Agreement with PIL (%)	45/55 =81.8%
Known Symptoms of Overdosage and Particulars of its Treatment	**If you take more EXFORGE than you should:**
1. There is no experience of overdose with Exforge yet.	N
2. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness.	N
3. Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.	N
4. If the ingestion is recent, induction of vomiting or gastric lavage may be considered.	N
5. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.	N
6. Clinically significant hypotension due to Exforge overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.	N
7. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.	N
8. Both valsartan and amlodipine are unlikely to be removed by haemodialysis.	N

Information Agreement with PIL (%)	0/8 =0%

Appendix 1.4

Medicine: MICARDIS	
INFORMATION CONTAINED IN THE PI	**PRESENCE OF INFORMATION IN THE PIL** **Yes (Y), No (N)**
Composition **1. MICARDIS 40 mg:** Each tablet contains 40 mg telmisartan. **2. MICARDIS 80 mg:** Each tablet contains 80 mg telmisartan. 3. Inactive ingredients: Povidone, meglumine, sodium hydroxide, sorbitol, magnesium stearate.	**WHAT MICARDIS TABLETS CONTAIN** Y Y Y
Information Agreement with PIL (%)	3/3 =100%
Indications 1. Treatment of mild to moderate hypertension, either alone or in combination with hydrochlorothiazide.	**WHAT MICARDIS IS USED FOR** Y
Information Agreement with PIL (%)	1/1 =100%
Contraindications 1. Hypersensitivity to any of the components of MICARDIS. 2. A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines. 3. Hereditary or idiopathic angioedema. 4. Hypertrophic obstructive cardiomyopathy (HOCM). 5. Bilateral renal artery stenosis. 6. Renal artery stenosis in patients with a single kidney. 7. Aortic stenosis. 8. Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride. 9. Porphyria. 10. Thiazide diuretics in (fixed dose) combination with MICARDIS (e.g. CO-MICARDIS) should not be given to patients with Addison's disease. This therapy is also contra-indicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.	**BEFORE YOU TAKE MICARDIS TABLETS** Y Y N N Y N Y Y Y N Y

11. Lithium therapy: Concomitant administration with MICARDIS may lead to toxic blood concentrations of lithium. 12. Pregnancy and lactation (see **WARNINGS** and **PREGNANCY AND LACTATION**). 13. Severe hepatic impairment. 14. Biliary obstructive disorders. 15. In case of rare hereditary conditions that may be incompatible with sorbitol, an excipient of the product, the use of MICARDIS is contra-indicated (please refer to SPECIAL PRECAUTIONS).	Y Y Y Y
Information Agreement with PIL (%)	11/15 =73.3%
Warnings ***1. Should a woman* become *pregnant while receiving MICARDIS, the treatment should be stopped promptly and an alternate medicine used.*** ***2. Should a woman contemplate pregnancy, the doctor should consider alternative medication.***	**Take special care with MICARDIS and tell your doctor if you:** Y Y
Information Agreement with PIL (%)	2/2 =100%
Interactions 1. MICARDIS may increase the hypotensive effect of other antihypertensive agents. 2. Co-administration of MICARDIS did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, paracetamol, ibuprofen, simvastatin and amlodipine. 3. For digoxin a 20 % increase in median plasma digoxin trough concentration has been observed (in a single case a 39 %). 4. Monitoring of plasma digoxin levels should be considered. 5. In one study the co-administration of MICARDIS and ramipril led to an increase of up to 2,5 fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known. 6. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with MICARDIS. 7. Careful monitoring of serum lithium levels is recommended during concomitant use. 8. Concomitant treatment with NSAIDs (including aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. 9. Compounds acting on the renin-angiotensin-system like MICARDIS may have synergistic effects.	**Taking other medicines with MICARDIS:** N N N N Y Y N Y N

10. Patients receiving NSAIDs and MICARDIS should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. 11. A reduced effect of antihypertensive medicines like MICARDIS by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.	N N
Information Agreement with PIL (%)	3/11 =27.3%
Pregnancy and Lactation 1. MICARDIS is contra-indicated during pregnancy- refer to WARNINGS. 2. A switch to a suitable alternative class of antihypertensive treatment should be carried out in advance of a planned pregnancy. 3. Fertile women should use adequate contraception. Refer to WARNINGS and CONTRA-INDICATIONS. 4. Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity. 5. Exposure to angiotensin II receptor antagonists (such as MICARDIS) during pregnancy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). 6. When pregnancy is diagnosed, treatment with MICARDIS should be stopped immediately, and, if appropriate, alternative therapy should be started. 7. Should exposure to MICARDIS have occurred during pregnancy, ultrasound check of renal function and skull is recommended. 8. Infants whose mothers have taken MICARDIS should be closely observed for hypotension. 9. MICARDIS is contra-indicated during lactation since it is not known whether it is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk.	**Pregnancy and breast-feeding:** Y Y N N N Y N N Y
Information Agreement with PIL (%)	4/9 =44.4%
Dosage and Directions for Use **DOSAGE AND DIRECTIONS FOR USE:** *Adults;* 1. The recommended dose is 40 mg once daily. 2. Some patients may already benefit at a daily dose of 20 mg. 3. In cases where the target blood pressure is not achieved, the MICARDIS dose can be increased to a maximum of 80 mg once daily.	**HOW TO TAKE MICARDIS** Y N Y

4. Alternatively, MICARDIS may be used in combination with a low dose thiazide diuretic such as hydrochlorothiazide 12,5 mg, which has been shown to have an additive blood pressure lowering effect with MICARDIS. 5. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment. *Renal impairment:* 6. No dosage adjustment is required for patients with renal impairment, including those on haemodialysis. *Hepatic impairment:* 7. In patients with mild to moderate hepatic impairment the dosage should not exceed 40 mg once daily. *Elderly:* 8. No dosing adjustment is necessary. *Children and adolescents up to 18 years:* 9. MICARDIS is not recommended for use in children below 18 years due to limited data on safety and efficacy.	Y N N N N Y
Information Agreement with PIL (%)	4/9 =44.4%
Side Effects and Special Precautions <u>SIDE EFFECTS</u> *1. The overall incidence of adverse events reported with MICARDIS (41,4 %) was usually comparable to placebo (43,9 %) in placebo controlled trials. The incidence of adverse events was not dose related and showed no correlation with gender, age or race of the patients.* *2. The following frequency classification is used:* *very common ≥ 1/10; common ≥ 1/100 and < 1/10; uncommon ≥ 1/1 000 and < 1/100; rare ≥ 1/10 000 and < 1/1 000; very rare < 1/10 000.* ***Infections and infestations:*** *3. Uncommon: Urinary tract infections (including cystitis), upper respiratory tract infections* ***Blood and the lymphatic systemic disorders:*** *4. Uncommon: anaemia* *5. Rare: thrombocytopenia* ***Immune system disorders:*** *6. Rare: hypersensitivity* ***Metabolism and nutritional disorders:***	**POSSIBLE SIDE-EFFECTS** N Y Y Y Y Y

7. Uncommon: hyperkalaemia	Y
***Psychiatric disorders**:*	
8. Uncommon: depression, insomnia	Y
9. Rare: anxiety	Y
Nervous system disorders:	
10. Uncommon: syncope/ fainting	Y
Eye disorders:	
11. Rare: visual disturbance	Y
Ear and labyrinth disorders:	
12. Uncommon: vertigo	Y
Cardiac disorders:	
13. Uncommon: bradycardia	Y
14. Rare: tachycardia	N
Vascular disorders:	
15. Uncommon: hypotension, orthostatic hypotension	Y
Respiratory, thoracic and mediastinal disorders:	
16. Uncommon: dyspnoea	Y
Gastro-intestinal disorders:	
17. Uncommon: abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting	Y
18. Rare: dry mouth, stomach discomfort	Y
Hepato-biliary disorders:	
19. Rare: hepatic function abnormal/liver disorder	Y
Skin and subcutaneous tissue disorders:	
20. Uncommon: increased sweating (hyperhidrosis), pruritus, rash	Y
21. Rare: eczema, erythema, angio-oedema, drug eruption, toxic skin eruption	Y
Musculoskeletal, connective tissue and bone disorders:	
22. Uncommon: back pain, muscle spasms {cramps in legs), myalgia	Y
23. Rare: arthralgia, pain in extremity (leg pain)	Y
Renal and urinary disorders:	
24. Uncommon: renal impairment including acute renal failure	Y
General disorders and administration site conditions:	
25. Uncommon: chest pain, asthenia (weakness)	Y
26. Rare: influenza-like symptoms	Y
Investigations:	

27. Uncommon: blood creatinine increased	Y
28. Rare: haemoglobin decreased, blood uric acid increased, hepatic enzymes increased, blood creatinine phosphokinase increased *The frequencies of side-effects which have been spontaneously reported since the introduction of MICARDIS into the market cannot be calculated and therefore their frequency is indicated as "not known".*	N
Infections and infestations:	Y
29. Not known: sepsis including fatal outcome	Y
Blood and the lymphatic systemic disorders:	
30. Not known: eosinophilia	N
Immune system disorders:	
31. Not known: anaphylactic reaction	Y
Skin and subcutaneous tissue disorders:	
32. Not known: urticaria	Y
Musculoskeletal, connective tissue and bone disorders:	
33. Not known: tendon pain (tendinitis like symptoms)	Y
Special precautions: ***Pregnancy:*** 34. MICARDIS should not be initiated during pregnancy.	Y
35. Patients planning pregnancy should be changed to alternative classes of antihypertensive medicines which have an established safety profile for use in pregnancy.	Y
36. When pregnancy is diagnosed, treatment with MICARDIS should be stopped immediately and, if appropriate, alternative therapy should be started.	Y
Renovascular hypertension: ***37.*** There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.	Y
Renal impairment and kidney transplant: 38. When MICARDIS is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of MICARDIS in patients with a recent kidney transplant.	Y
Intravascular volume depletion:	

39. Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/ or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions, especially volume and/or sodium depletion, should be corrected before administration of MICARDIS.	Y
Dual blockade of the renin-angiotensin-aldosterone system: 40. Combining medicines which inhibit the renin-angiotensin-aldosterone system can lead to changes in renal function (including acute renal failure) in susceptible individuals.	Y
41. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist like MICARDIS) should therefore be undertaken cautiously in individual cases only and should be accompanied by dose monitoring of renal function.	Y
Other conditions with stimulation of the renin-angiotensin-aldosterone system: 42. In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.	N
Primary aldosteronism: 43. Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of MICARDIS Is not recommended.	Y
Aortic and mitral valve* stenosis, *obstructive hypertrophic cardiomyopathy: 44. As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.	Y
Hyperkalaemia: 45. During treatment with other medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. 46. Monitoring of serum potassium in patients at risk is recommended.	Y
47. Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with MICARDIS.	N
Hepatic impairment:	Y

48. MICARDIS is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. MICARDIS should be used with caution in these patients- see CONTRA-INDICATIONS. 49. MICARDIS should be used only with caution in patients with mild to moderate hepatic impairment. ***Sorbitol:*** 50. MICARDIS contains 338 mg of sorbitol per maximum recommended daily dose. 51. Patients with the rare hereditary condition of fructose intolerance should not take this medicine. ***Other:*** 52. Angiotensin receptor blockers, including MICARDIS, are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population. 53. Excessive reduction in blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke. ***Effects on ability to drive and use machines:*** 54. No studies on the effect on the ability to drive and use machines have been performed, 55. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when tailing antihypertensive therapy.	N Y N Y N N N Y
Information Agreement with PIL (%)	44/55 =80%
Known Symptoms of Overdosage and Particulars of its Treatment 1. Limited information is available with regard to overdose in humans. 2. The most prominent manifestations of MICARDIS overdose were hypotension and tachycardia; bradycardia also occurred. 3. If symptomatic hypotension should occur, supportive treatment should be instituted. 4. MICARDIS is not removed by haemodialysis.	**If you take more MICARDIS than you should:** N N N N
Information Agreement with PIL (%)	0/4 =0%

Appendix 1.5

Medicine: TWYNSTA	
INFORMATION CONTAINED IN THE PI	**PRESENCE OF INFORMATION IN THE PIL** **Yes (Y), No (N)**
COMPOSITION **1. TWYNSTA 40/5 mg tablets:** Each tablet contains 40 mg telmisartan and 5 mg amlodipine base (as besylate salt). **2. TWYNSTA 40/10 mg tablets:** Each tablet contains 40 mg telmisartan and 10 mg amlodipine base (as besylate salt). **3. TWYNSTA 80/5 mg tablets:** Each tablet contains 80 mg telmisartan and 5 mg amlodipine base (as besylate salt). **4. TWYNSTA 80/10 mg tablets:** Each tablet contains 80 mg telmisartan and 10 mg amlodipine base (as besylate salt). **5. Inactive ingredients:** Colloidal anhydrous silica, FD&C blue No. 1 aluminium lake, ferric oxide black, ferric oxide yellow, magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinised starch, sodium hydroxide, sorbitol.	**WHAT TWYNSTA CONTAINS** Y Y Y Y Y
Information Agreement with PIL (%)	5/5 =100%
INDICATIONS **1. Replacement therapy:** Treatment of essential hypertension in patients who have been stabilised on the two component medicines used at the same dose. **2. Add on therapy:** TWYNSTA is indicated in patients whose blood pressure is not adequately controlled on amlodipine monotherapy.	**WHAT TWYNSTA IS USED FOR** Y Y
Information Agreement with PIL (%)	2/2 =100 %
CONTRAINDICATIONS 1. Hypersensitivity to any of the components of TWYNSTA 2. Hypersensitivity to dihydropyridine derivatives 3. A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines 4. Hereditary or idiopathic angioedema 5. Hypertrophic obstructive cardiomyopathy (HOCM) 6. Severe renal function impairment (creatinine clearance less than 30 ml/min) 7. Bilateral renal artery stenosis 8. Renal artery stenosis in patients with a single kidney	**BEFORE YOU TAKE TWYNSTA** Y Y Y **N** Y Y Y Y

9. Aortic stenosis 10. Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride 11. Porphyria 12. Lithium therapy: Concomitant administration with TWYNSTA may lead to toxic blood concentrations of lithium 13. Pregnancy and lactation (see **WARNINGS** and **PREGNANCY AND LACTATION**) 14. Biliary obstructive disorders 15. Severe hepatic impairment 16. Cardiogenic shock 17. In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of TWYNSTA is contra-indicated. TWYNSTA contains sorbitol. (Please refer to **Special precautions**).	Y Y Y Y **N** Y Y Y Y
Information Agreement with PIL (%)	5/17 = 88.2%
Warnings 1. Should a woman become pregnant while receiving TWYNSTA, the treatment should be stopped promptly and switched to a different class of medicine. (See CONTRA-INDICATIONS and PREGNANCY AND LACTATION).	N
Information Agreement with PIL (%)	0/1 =0%
Interactions 1. No interactions between the two components of the fixed dose combinations have been observed in clinical studies. **Interactions common to the combination:** 2. No interaction studies have been performed with TWYNSTA and other medicinal products. **To be taken into account with concomitant use:** *Other antihypertensive agents:* 3. The blood pressure lowering effect of TWYNSTA can be increased by concomitant use of other antihypertensive medicinal products. *Agents with blood pressure lowering potential:* 4. Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of TWYNSTA: e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants. *Corticosteroids (systemic route):*	N N Y Y Y

5. Reduction of the antihypertensive effect.	
Interactions linked to the telmisartan component of TWYNSTA: 6. Telmisartan may increase the hypotensive effect of other antihypertensive agents. Other interactions of clinical significance have not been identified.	Y
7. Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20 % increase in median plasma digoxin trough concentration has been observed (39 % in a single case); monitoring of plasma digoxin levels should be considered. In one study the co-administration of telmisartan and ramipril led to an increase of up to 2,5 fold in the AUC0-24 and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.	N
8. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with telmisartan.	Y
9. Treatment with NSAIDs (i.e. aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated.	N
10. Compounds acting on the renin-angiotensin-system like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.	N
11. A reduced effect of antihypertensive medicines like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.	Y
Interactions linked to the amlodipine component of TWYNSTA: **Concomitant use requiring caution:** *CYP3A4 inhibitors:* 12. A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50 % and the effect of amlodipine is increased).	N
13. The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.	N
14. CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum): Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.	Y
Concomitant use to be taken into account: *Others:*	

15. In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect. *Additional information:* 16. Concomitant administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine. 17. Co-administration of amlodipine with cimetidine had no significant effect on the pharmacokinetics of amlodipine. 18. Co-administration of amlodipine with atorvastatin, digoxin, warfarin or cyclosporin had no significant effect on the pharmacokinetics or pharmacodynamics of these agents.	N N N N
Information Agreement with PIL (%)	7/18 = 38.9%
Pregnancy and Lactation 1. TWYNSTA should not be used during pregnancy and lactation. Effects related to the mono components are described below. **Pregnancy:** **Telmisartan:** 2. The use of TWYNSTA is contra-indicated during pregnancy. When pregnancy is planned or confirmed, TWYNSTA should be discontinued as soon as possible. Refer to **CONTRA- INDICATIONS** and **WARNINGS**. 3. Exposure to medicines affecting the renin-angiotensin-system, such as TWYNSTA, during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). 4. Women of childbearing age should ensure adequate contraception. 5. Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. 6. When pregnancy is diagnosed, treatment with TWYNSTA should be stopped immediately, and, if appropriate, alternative therapy should be started. 7. Should exposure to TWYNSTA have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. 8. Infants whose mothers have taken TWYNSTA should be closely observed for hypotension. **Lactation:** 9. It is not known whether telmisartan and/or amlodipine (as in TWYNSTA) are excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk.	**Pregnancy and breast-feeding:** Y Y N N Y N N N

10. Because of the potential adverse reactions in breastfed infants, TWYNSTA should not be used by breast feeding mothers.	Y
Information Agreement with PIL (%)	4/10 = 40%
Dosage and Directions for Use 1. TWYNSTA should be taken once daily. **Replacement Therapy:** 2. Patients taking telmisartan and amlodipine as separate tablets can instead take TWYNSTA containing the same component doses in one tablet once daily. **Add on therapy:** 3. TWYNSTA may be administered in patients whose blood pressure is not adequately controlled with amlodipine alone. 4. The usual starting dose of TWYNSTA is 40/5 mg once daily. 5. If additional blood pressure lowering is needed after at least 2 weeks of therapy, the dose may be titrated up to a maximum of 80/10 mg once daily. 6. TWYNSTA may be taken with or without food. **Renal impairment:** 7. No dosage adjustment is required for patients with mild to moderate renal impairment (see **Special precautions**). Amlodipine and telmisartan are not dialysable. **Hepatic impairment:** 8. In patients with mild to moderate hepatic impairment TWYNSTA should be administered with caution. For telmisartan the dose should not exceed 40/5 mg or 40/10 mg once daily. **Elderly:** 9. No dose adjustment is necessary for elderly patients. **Children and adolescents:**	Y N N N N Y N Y N

10. TWYNSTA is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.	N
Information Agreement with PIL (%)	3/10 = 30%
Side Effects and Special Precautions **Side-Effects:** ***Fixed Dose Combination:*** 1. The safety and tolerability of TWYNSTA has been evaluated in five controlled clinical studies with over 3 500 patients, over 2 500 of whom received telmisartan in combination with amlodipine. The following frequency classification is used: very common ≥ 1/10; common ≥ 1/100 and < 1/10; uncommon ≥ 1/1 000 and < 1/100; rare ≥ 1/10 000 and < 1/1 000; very rare < 1/10 000. **Infections and infestations:** 2. Rare: cystitis **Psychiatric disorders:** 3. Rare: depression, anxiety, insomnia **Nervous system disorders:** 4. Common: dizziness 5. Uncommon: somnolence, migraine, headache, paraesthesia 6. Rare: syncope (fainting), peripheral neuropathy, hypoaesthesia, dysgeusia, tremor **Ear and labyrinth disorders:** 7. Uncommon: vertigo **Cardiac disorders:** 8. Uncommon: bradycardia, palpitations **Vascular disorders:** 9. Uncommon: hypotension, orthostatic hypotension, flushing	**POSSIBLE SIDE EFFECTS** N Y Y Y Y Y Y Y Y

Respiratory, thoracic and mediastinal disorders:	
10. Uncommon: cough	Y
Gastro-intestinal disorders:	
11. Uncommon: abdominal pain, diarrhoea, nausea	Y
12. Rare: vomiting, gingival hypertrophy, dyspepsia, dry mouth	N
Skin and subcutaneous tissue disorders:	
13. Uncommon: pruritus	Y
14. Rare: eczema, erythema, rash	Y
Musculoskeletal, connective tissue and bone disorders:	
15. Uncommon: arthralgia, muscle spasms, myalgia	
16. Rare: back pain, pain in extremity	Y
	Y
Renal and urinary disorders:	
17. Rare: nocturia	
	Y
Reproductive system and breast disorders:	
18. Uncommon: erectile dysfunction	Y
General disorders:	
19. Common: oedema peripheral	N
20. Uncommon: asthenia, chest pain, fatigue, oedema	Y
21. Rare: malaise	Y
Investigations:	
22. Uncommon: hepatic enzymes increased	Y
23. Rare: blood uric acid increased	Y
The following side-effects are expected based on experience with telmisartan monotherapy, but the frequencies cannot be determined from the reference data set:	
Infections and infestations:	
24. Frequency not known: sepsis including fatal outcome, urinary tract infections, upper respiratory tract infections	Y
Blood and the lymphatic system disorders:	
25. Frequency not known: anaemia, eosinophilia, thrombocytopenia	Y

Immune system disorders: 26. Frequency not known: angioedema, anaphylactic reaction, hypersensitivity	Y
Metabolism and nutritional disorders: 27. Frequency not known: hyperkalaemia	Y
Eye disorders: 28. Frequency not known: visual disturbance	Y
Cardiac disorders: 29. Frequency not known: tachycardia	Y
Respiratory, thoracic and mediastinal disorders: 30. Frequency not known: dyspnoea	Y
Gastro-intestinal disorders: 31. Frequency not known: flatulence, stomach discomfort	Y
Hepato-biliary disorders: 32. Frequency not known: hepatic function abnormal, liver disorder	Y
Skin and subcutaneous tissue disorders: 33. Frequency not known: hyperhidrosis, urticaria, drug eruption, toxic skin eruption	Y Y
Musculoskeletal, connective tissue and bone disorders: 34. Frequency not known: tendon pain	
Renal and urinary disorders: 35. Frequency not known: renal impairment	Y
General disorders: 36. Frequency not known: influenza-like illness	Y
Investigations: 37. Frequency not known: haemoglobin decreased, blood creatinine increased, blood creatinine phosphokinase (CPK) increased.	Y

The following side-effects are expected based on experience with amlodipine monotherapy, but the frequencies cannot be determined from the reference data set:	
Blood and the lymphatic system disorders: 38. Frequency not known: thrombocytopenia	Y
Immune system disorders: 39. Frequency not known: angioedema, hypersensitivity	Y
Metabolism and nutritional disorders: 40. Frequency not known: hyperglycaemia	Y
Psychiatric disorders: 41. Frequency not known: mood change	Y
Eye disorders: 42. Frequency not known: visual impairment	Y
Ear and labyrinth disorders: 43. Frequency not known: tinnitus	Y
Cardiac disorders: 44. Frequency not known: myocardial infarction, dysrhythmia, ventricular tachycardia, atrial fibrillation	Y
Vascular disorders: 45. Frequency not known: vasculitis	Y
Respiratory, thoracic and mediastinal disorders: 46. Frequency not known: dyspnoea, rhinitis	Y
Gastro-intestinal disorders: 47. Frequency not known: change of bowel habit, pancreatitis, gastritis	Y
Hepato-biliary disorders: 48. Frequency not known: hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)	Y
Skin and subcutaneous tissue disorders: 49. Frequency not known: hyperhidrosis, urticaria, alopecia, purpura, skin discolouration, erythema multiforme	Y

Renal and urinary disorders: 50. Frequency not known: micturition disorder, pollakiuria	Y
Reproductive system and breast disorders: 51. Frequency not known: gynaecomastia	Y
General disorders: 52. Frequency not known: pain, weight increased, weight decreased	Y
Special precautions: **Pregnancy:**	
53.. TWYNSTA should not be initiated during pregnancy (see CONTRA-INDICATIONS).	N
54. Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.	N
55. When pregnancy is diagnosed, treatment with TWYNSTA should be stopped immediately, and if appropriate, alternative therapy should be started. (See WARNINGS and PREGNANCY AND LACTATION).	N
56. Hepatic impairment: Telmisartan (ingredient of TWYNSTA) is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. TWYNSTA should therefore be used with caution in patients with mild to moderate impairment of liver function and should not be used in patients with severe liver impairment – see CONTRA-INDICATIONS.	Y
57. Renovascular hypertension: There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system - see CONTRA- INDICATIONS.	Y
58. Renal impairment and kidney transplant: When TWYNSTA is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of TWYNSTA in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.	Y
59. Intravascular hypovolaemia:	

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of TWYNSTA.	N
60. Dual blockade of the renin-angiotensin-aldosterone system: As a consequence of inhibiting the renin-angiotensin-aldosterone system changes in renal function (including acute renal failure) have been reported, especially if combining medicinal products that affect this system.	Y
61. TWYNSTA can be administered with other antihypertensive medicines; however dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE inhibitor to TWYNSTA) is not recommended and should therefore be limited to individually defined cases with close monitoring of renal function.	N
62. Other conditions with stimulation of the renin-angiotensin-aldosterone system: In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with TWYNSTA, that affects this system, has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.	Y
63. Primary aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-system. Therefore, the use of TWYNSTA is not recommended.	Y
64. Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy: TWYNSTA is contra-indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy.	Y
65. Unstable angina pectoris, acute myocardial infarction: There are no data to support the use of TWYNSTA in unstable angina pectoris and during or within one month of a myocardial infarction.	Y
66. Heart failure: In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema.	Y
67. Hyperkalaemia: During treatment with TWYNSTA hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.	Y

68. Based on experience with the use of medicinal products that affect the renin-angiotensin- system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co- administered cautiously with TWYNSTA. **69. Sorbitol:** TWYNSTA tablets contain 337,28 mg of sorbitol per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine. **70. Other:** Excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease may result in a myocardial infarction or stroke. **71 Effects on the ability to drive and use machines:** No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as syncope (fainting), somnolence, dizziness, or vertigo during treatment. 72. Therefore, caution should be recommended when driving a vehicle or operating machinery. If patients experience these adverse effects, they should avoid potentially hazardous tasks such as driving or operating machinery.	Y N Y Y .
Information Agreement with PIL (%)	62/72 = 86.1 %
Known Symptoms of Overdosage and Particulars of its Treatment **Symptoms:** 1. There is no experience of overdose with TWYNSTA. 2. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. 3. The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia; bradycardia might also occur. 4. Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome may occur. **Therapy:** 5. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and amlodipine are not removed by haemodialysis.	**If you take more TWYNSTA than you should:** N N N N N
Information Agreement with PIL (%)	0/5 = 0%

APPENDIX 2

Fry's Readability Graphs

APPENDIX 2.1

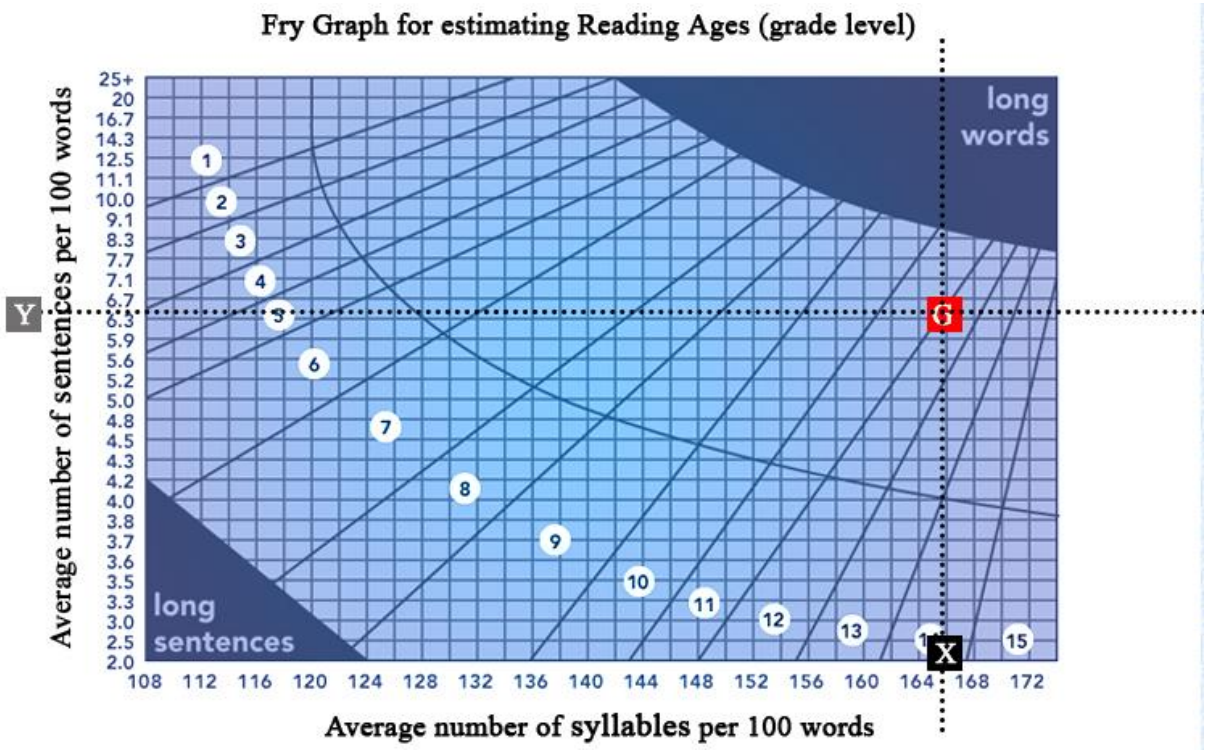
FRY GRAPHS- CO EXFORGE

NB: The number between the two parallel lines represents the U.S. grade level.

Section 1- What Co Exforge Contains

Sample text:
WHAT CO EXFORGE CONTAINS: The active substances of CO EXFORGE are amlodipine besylate, valsartan and hydrochlorothiazide. The other ingredients are cellulose microcrystalline: crospovidone; hypromellose; macrogol 4000; magnesium stearate; silica, colloidal anhydrous; talc. CO EXFORGE 5 mg/160 mg/12,5 mg contains in addition titanium dioxide (E171). CO EXFORGE 10 mg/160 mg/12,5 mg contains in addition titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E 172). CO EXFORGE 5 mg/160 mg/25 mg contains in addition titanium dioxide (E171), iron oxide, yellow (E172). CO EXFORGE 10 mg/160 mg/25 mg contains in addition iron oxide, yellow (E172). CO EXFORGE 10 mg/320 mg/25 mg contains in addition iron oxide, yellow (E172).

<u>Fry Graph</u>



Average # of syllables per 100 words: **165**
Average # of sentences per 100 words: **6.4**

 = 165

 = 6.4

 = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

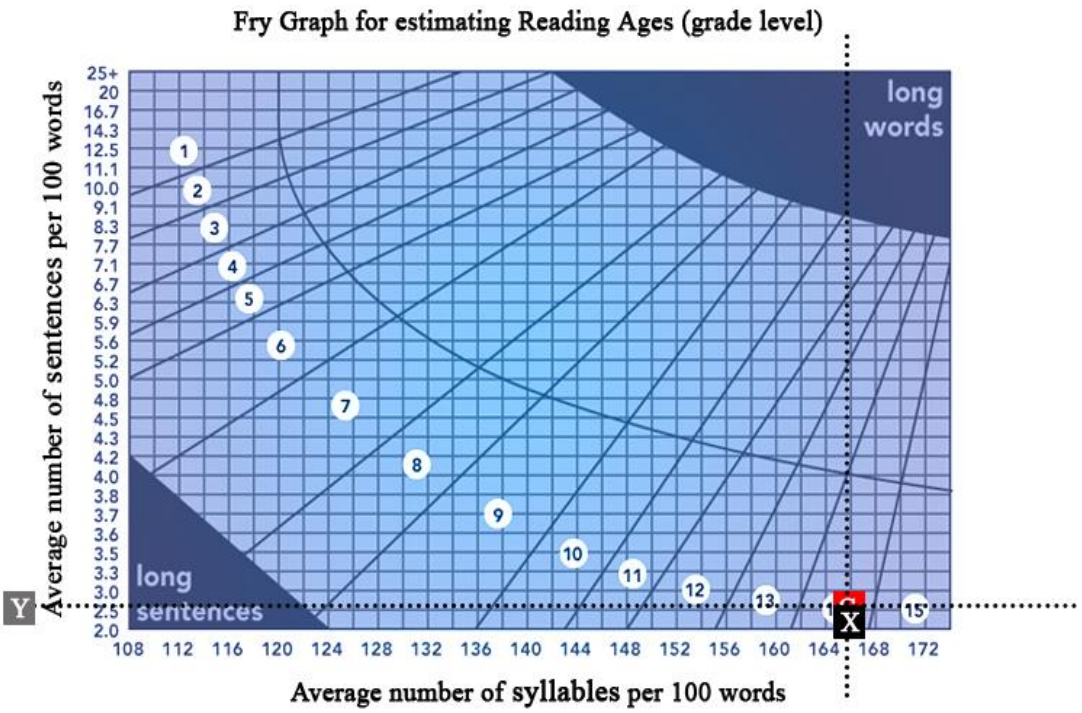
Section 2- What Co Exforge Is Used For

Sample text:

WHAT CO EXFORGE IS USED FOR: CO EXFORGE is used to treat high blood pressure in patients whose blood pressure is adequately controlled on the combination of the three medicines contained in CO EXFORGE, on individual doses. WHAT CO EXFORGE IS USED FOR: CO EXFORGE is used to treat high blood pressure in patients whose blood pressure is adequately controlled on the combination of the three medicines contained in CO EXFORGE, on individual doses. WHAT CO EXFORGE IS USED FOR: CO EXFORGE is used to treat high blood pressure in patients whose blood pressure is adequately controlled on the combination of the three medicines contained in CO EXFORGE, on individual doses.

*A sample size of minimum 100 words needs to be plotted on the graph. As this section of the PIL contains text below this, the text had to be repeated.

Fry Graph



Average # of syllables per 100 words: **165**
Average # of sentences per 100 words: **2.7**

X = 165

Y = 2.7

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

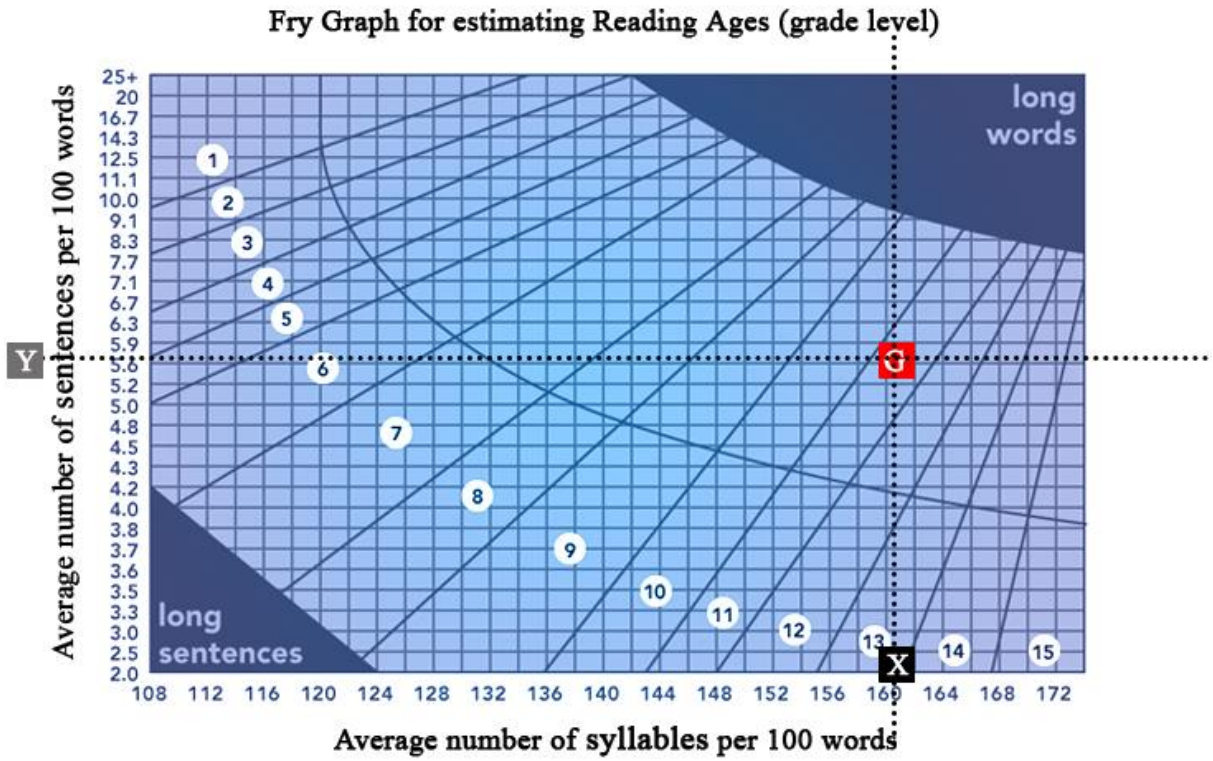
Section 3.1 – Before You Take Co Exforge

Sample text:

BEFORE YOU TAKE CO EXFORGE: Follow all the doctors instructions carefully. Do not take CO EXFORGE: • If you are allergic (hypersensitive) to amlodipine, valsartan, hydrochlorothiazide or sulfonamides or any of the other ingredients of CO EXFORGE. • If you are pregnant or planning to become pregnant, or breastfeeding your baby. • If you have serious liver or kidney disease or impairment. • If you have inability to produce urine. • If you have only one kidney or you suffer from or a narrowing or blockage of the arteries that supply blood to your kidney. • If you have porphyria, a rare disease of a deficiency of certain enzymes. The disease can be recognised by nerve pain and skin problems. • If you have a too low a level of potassium or sodium in your blood, or if you have a too high level of calcium in your blood despite treatment. • If you have uric acid crystals in the joints (gout). • If you have imbalances in your blood chemistry, such as low sodium and potassium levels, or high calcium or urea levels. • If you are taking any medicine that contain lithium. • If you are taking other medicines or substances, which increase the potassium levels in your blood (such as certain types of diuretics, such as spironolactone, triamterene, amiloride and potassium supplements,. These medicines are usually used to treat high blood pressure or swelling. • If you suffer from

a narrowing of valves in your heart (called aortic or mitral stenosis), or abnormally increased thickness of your heart muscle with narrowing (called obstructive hypertrophic cardiomyopathy. ◆ If you have previously suffered from the rapid swelling of the skin or mucous membranes of the face (angioedema) while taking this type of medicines, called angiotensin receptor blockers (ARBs). This reactions can also occur without any apparent reason or can be hereditary. ◆ If you have Addison◆s disease, a rare, chronic disease of the adrenal glands. ◆ If any of these apply to you, tell your doctor before taking CO EXFORGE.

Fry Graph



Average # of syllables per 100 words: **160**
Average # of sentences per 100 words: **5.8**

X = 160

Y = 5.8

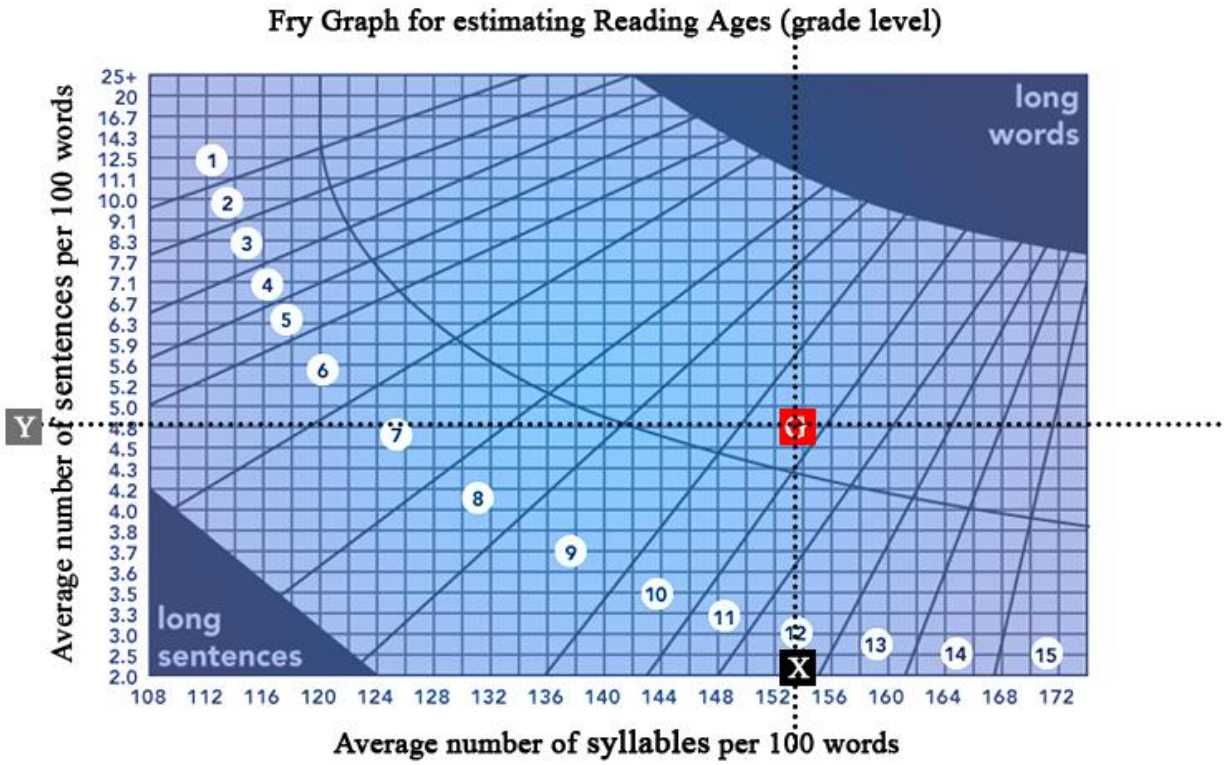
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.2 – Before You Take Co Exforge continued

Sample text:
Take special care with CO EXFORGE: ◆ Your doctor may wish to have your blood tested before and at regular intervals during your treatment to check the values of potassium, magnesium, calcium, sodium, sugar, cholesterol, uric acid and the amounts of red and white cells as well as platelets. ◆ If you are taking already a diuretic (a medicine to increase the

amount of urine you produce). • If you have fever, facial rash, and joint pain, which may be signs of lupus erythematosus (or a history of this disease). • If you have diabetes (high blood sugar). • If you have been told you have high levels of calcium, cholesterol or triglycerides in your blood. • If you have been told you have low levels of potassium or magnesium in your blood, • If you suffer from a liver disorder. • If you are suffering from several episodes of vomiting or diarrhoea. • One of the ingredients of CO EXFORGE is hydrochlorothiazide, a thiazide diuretic. This ingredient may change a person•s glucose tolerance (this is used to determine your resistance to glucose and is used to test for diabetes) and raise the levels of cholesterol, triglycerides (fatty acid in the blood), and uric acid (a component in your blood formed from the breakdown of proteins). If any of these apply to you, tell your doctor before taking CO EXFORGE. • If you experience dizziness and/or faintness during treatment with CO EXFORGE. • If you get any of these symptoms, tell your doctor as soon as possible. Children and adolescents (below 18 years): The use of CO EXFORGE in children and adolescents is not recommended. Taking CO EXFORGE with food and drink: You can take CO EXFORGE with or without food.

Fry Graph



Average # of <u>syllables</u> per 100 words: **153**
Average # of <u>sentences</u> per 100 words: **4.8**

X = 153

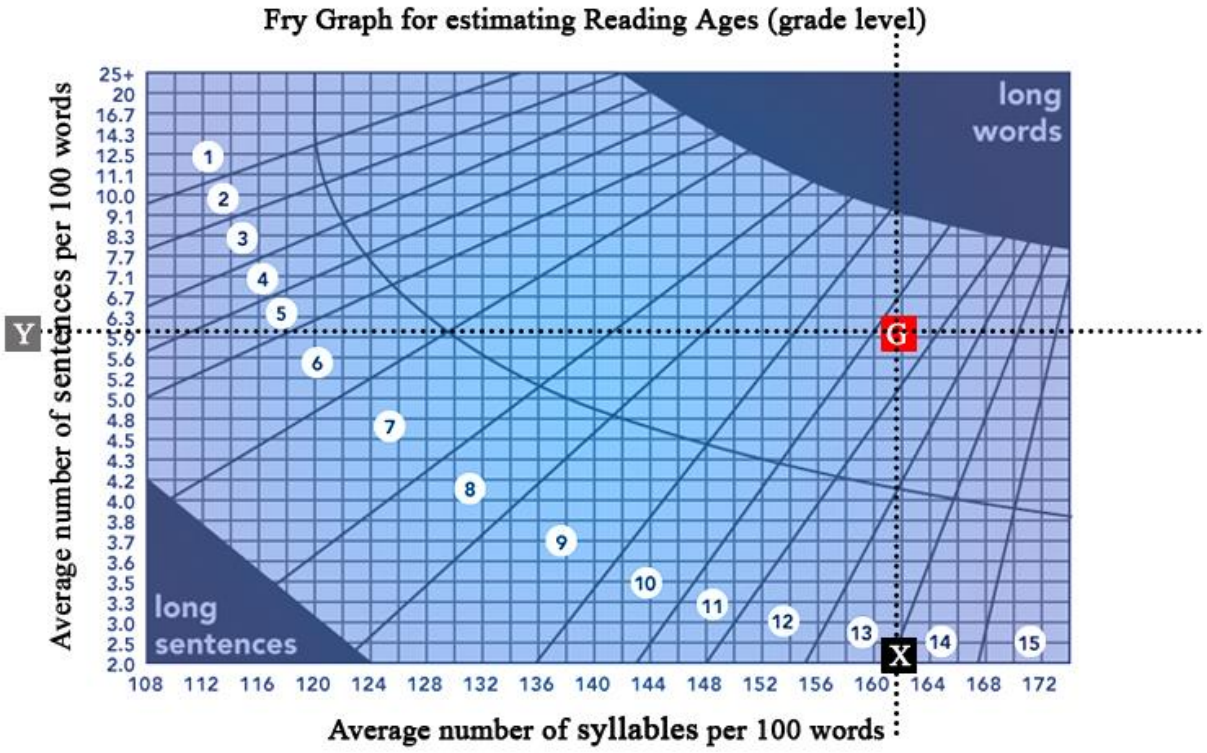
Y = 4.8

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.3 – Before You Take Co Exforge continued

Sample text:
Pregnancy and breast-feeding: Do not take CO EXFORGE if you are pregnant or planning to become pregnant. Use during pregnancy may cause serious damage to your unborn child. It is therefore important to check with your doctor immediately if you think you may have become pregnant or are planning to become pregnant. Your doctor will discuss with you the potential risk of taking CO EXFORGE during pregnancy. Tell your doctor if you are breast-feeding. Treatment with CO EXFORGE is not recommended during breast-feeding (see "Do not take CO EXFORGE"). Driving and using machines: CO EXFORGE may cause dizziness and affect the ability to concentrate. So before you drive a vehicle, use machinery, or carry out other activities that require concentration, make sure you know how you react to the effects of CO EXFORGE.

Fry Graph



Average # of syllables per 100 words: **161**
Average # of sentences per 100 words: **5.9**

X = 161

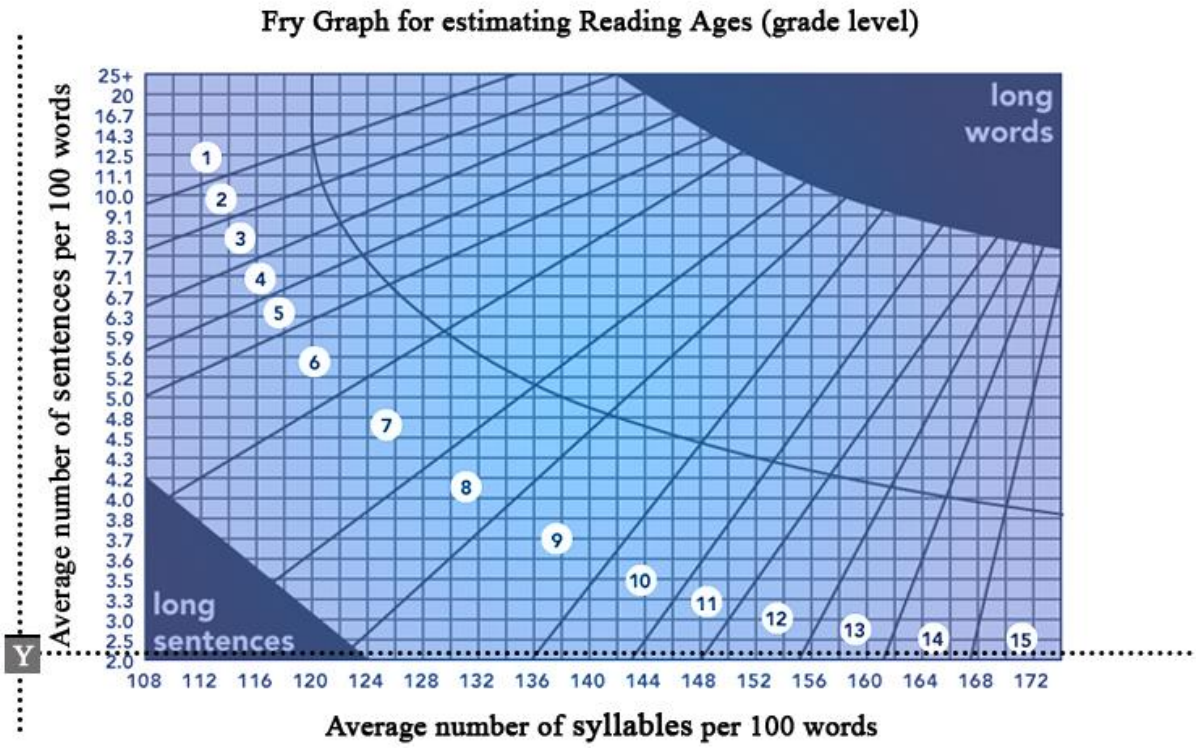
Y = 5.9

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.4 – Before You Take Co Exforge continued

Sample text:
Taking other medicines with CO EXFORGE: If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of CO EXFORGE with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional, for advice. Tell your doctor or a pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes in particular: • Potassium-sparing medicines, potassium supplements, or salt substitutes containing potassium; • some medicines used to treat infections such as amphotericin, penicillin G; • medicines used for oesophageal ulceration and inflammation (carbenoxolone); • medicines used to lower blood pressure; • lithium, a medicine used to treat some psychological conditions; • medicines used to relieve pain or inflammation, especially nonsteroidal anti-inflammatory agents; • cortisone-like medicines, steroids; • digoxin (a heart medicine); • muscle relaxant medicines used during operations; • allopurinol (anti-gout treatment); • amantadine (anti-Parkinson therapy, also used for influenza treatment); • cytotoxic medicines (cancer therapy); • anticholinergic agents (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia); • ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g: rheumathoid arthritis or atopic dermatitis); • insulin or antidiabetic medicines taken by mouth; • cholestyramine and colestipol (resins used mainly to treat high levels of lipids in the blood); • vitamin D and calcium salts; • carbamazepine (anticonvulsant and mood stabilising medicine used primarily in the treatment of epilepsy and bipolar disorder). • Avoid alcohol until you have talked to your doctor. Alcohol may make blood pressure fall more and/or increase the possibility of dizziness or fainting.

Fry Graph



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of syllables per 100 words: **208**
Average # of sentences per 100 words: **2.4**

X = 208

Y = 2.4

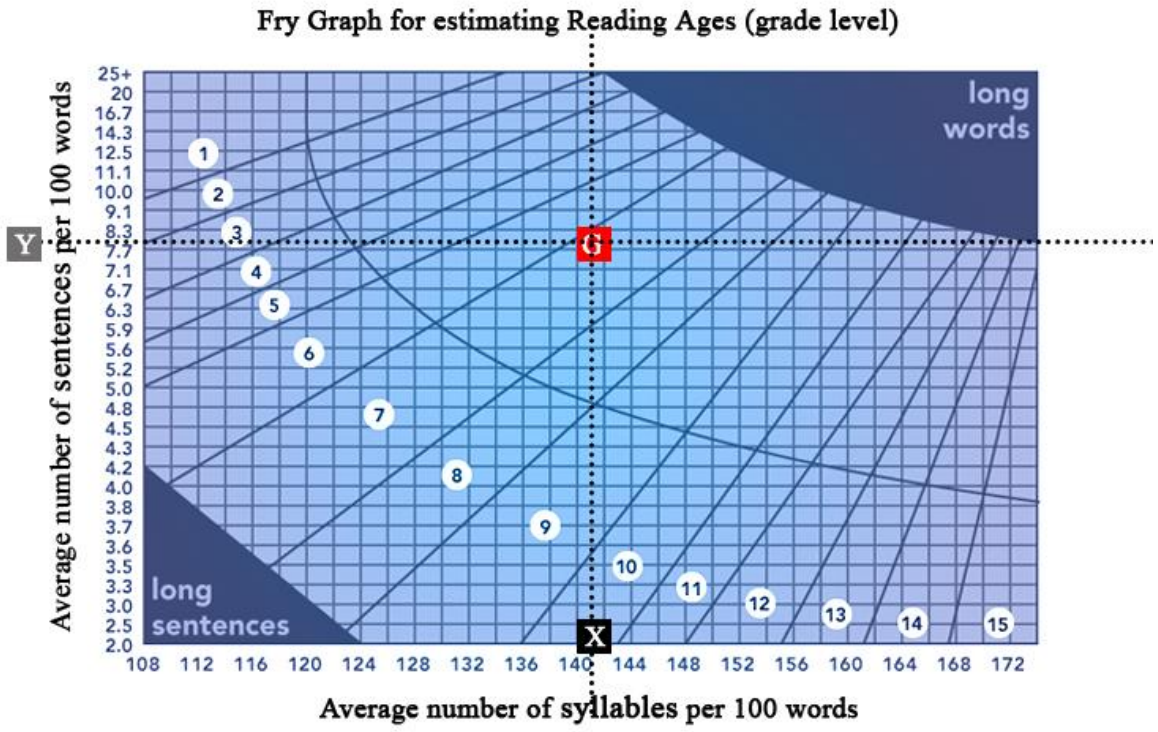
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 4.1 – How to Take Co Exforge

Sample Text:

HOW TO TAKE CO EXFORGE: Do not exceed the recommended dose. Follow your doctor's instructions carefully. CO EXFORGE is for oral use only. How much CO EXFORGE to take: Your doctor will tell you exactly how many tablets of CO EXFORGE you should take. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of CO EXFORGE is too strong or too weak, talk to your doctor or pharmacist. Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose. The recommended dose of CO EXFORGE is one film coated tablet per day. Older people (over 65 years): There are no special dose recommendations for patients aged 65 years or older.

Fry Graph



Average # of syllables per 100 words: **141**
Average # of sentences per 100 words: **7.8**

X = 141

Y = 7.8

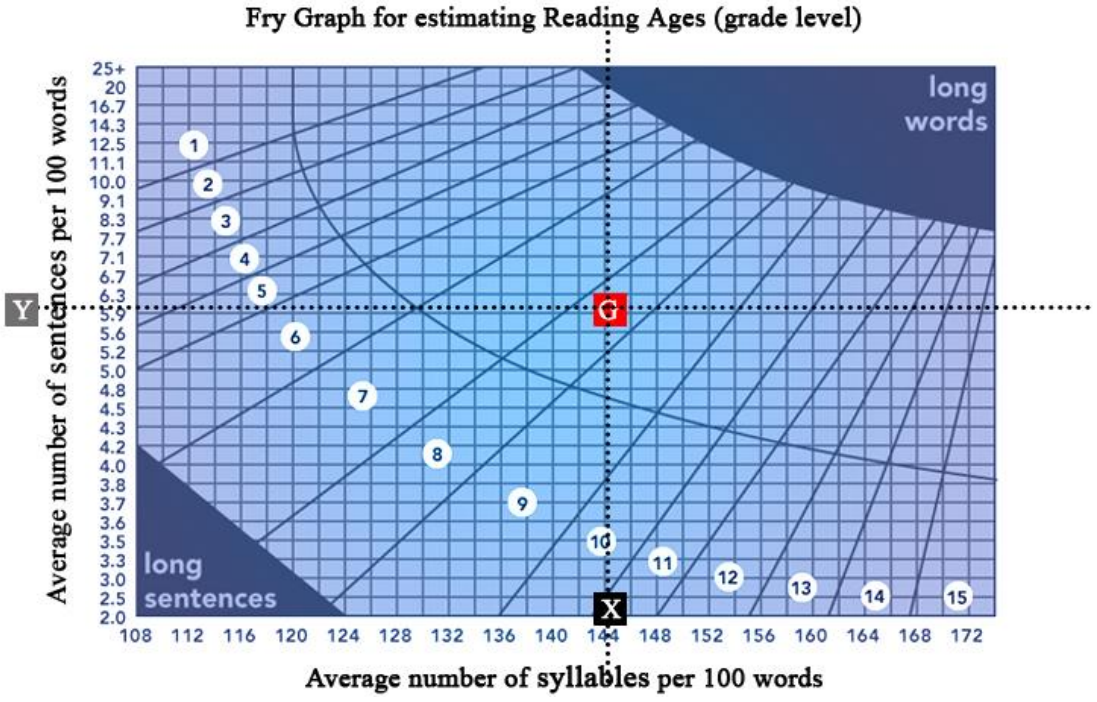
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 4.2 – How to Take Co Exforge continued

Sample Text:

When to take CO EXFORGE: Taking CO EXFORGE at the same time each day will help you remember when to take your medicine. How to take CO EXFORGE: CO EXFORGE may be taken with or without food. Swallow the tablets with a glass of water. If a tablet show signs of cracking the tablet should not be taken. How long to take CO EXFORGE: Continue taking CO EXFORGE as your doctor tells you. If you have questions about how long to take CO EXFORGE, talk to your doctor or your pharmacist. If you take more CO EXFORGE than you should: If you have accidentally taken too many tablets of CO EXFORGE, consult your doctor or pharmacist immediately. If neither is available, seek help at the nearest hospital or poison control center. If you forget to take CO EXFORGE: It is advisable to take your medicine at the same time each day, preferably in the morning. If you forget to take CO EXFORGE, take it as soon as you remember and then take your next dose at its usual time. However, if it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for the forgotten tablet. If you stop taking CO EXFORGE: Stopping your treatment with CO EXFORGE may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.

Fry Graph



Average # of syllables per 100 words: **144**
Average # of sentences per 100 words: **5.9**

X = 144

Y = 5.9

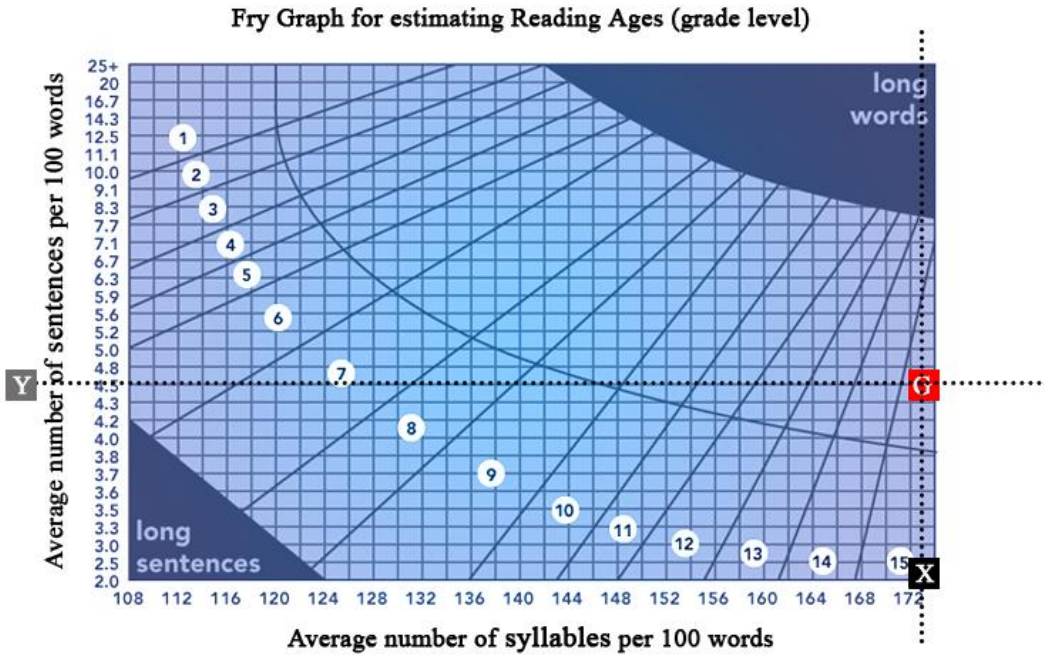
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.1 – Possible Side Effects

Sample Text:

POSSIBLE SIDE EFFECTS: Not all side effects reported for CO EXFORGE are included in this leaflet. Should your general health worsen while taking CO EXFORGE, please consult your doctor, pharmacist or other health care professional for advice. CO EXFORGE can have side effects. Some side effects can be serious. Allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing or swallowing, dizziness; low blood pressure with symptoms such as dizziness, light-headedness; sudden loss of consciousness. If you experience any of these, tell your doctor immediately. Possible side effects of CO EXFORGE include: Frequent: Flu-like symptoms; nasal congestion, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; feeling sleepy; dizziness; nausea; decreased appetite; inability to obtain an erection (impotence); fast heart beat (palpitations); faintness on standing up, which may be worsened by alcohol or sedatives; hives and other forms of skin rash; changes in blood chemistry; redness and warm feeling of the face and/or the neck; weakness, stomach discomfort after meal.

Fry Graph



Average # of syllables per 100 words: **172**
Average # of sentences per 100 words: **4.5**

X = 172

Y = 4.5

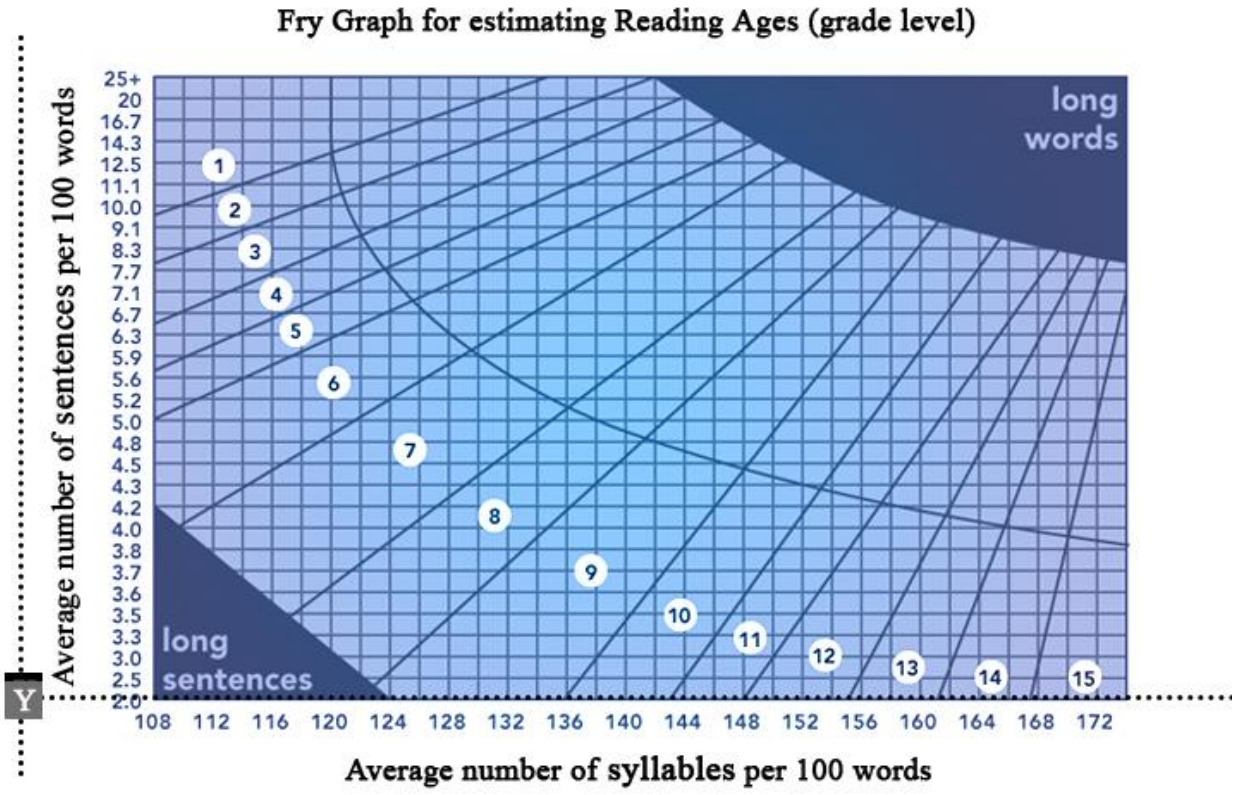
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.2 – Possible Side Effects continued

Sample Text:

Less frequent: Stomach pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo (feeling dizzy); cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints; visual disturbance, anxiety; tinnitus (ringing in the ears); passing more urine than normal or feeling an increased urge to pass urine; inability to get or maintain an erection; sensation of heaviness; excessive sweating; generalised skin rash; itching; muscle spasm; fever, sore throat or mouth ulcers due to infections (symptoms of low level of white blood cells also called leucopenia,

Fry Graph



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of syllables per 100 words: **173**
Average # of sentences per 100 words: **1.1**

X = 173

Y = 1.1

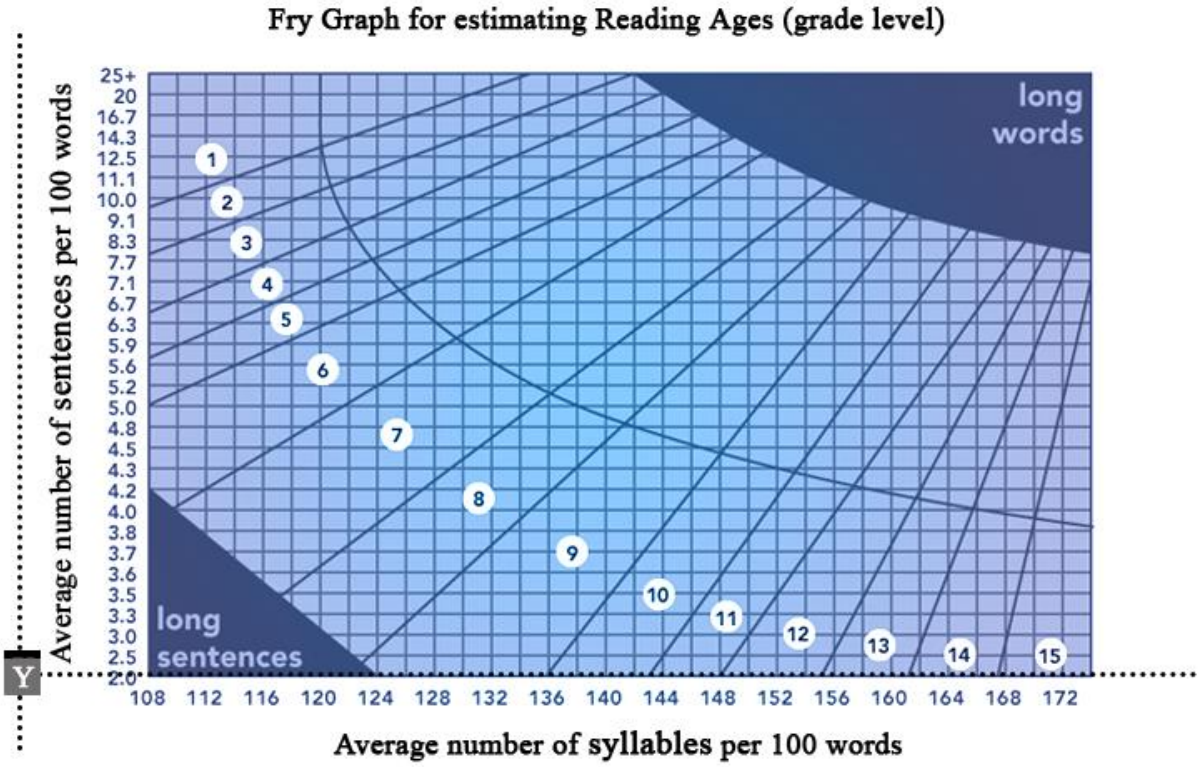
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.3 – Possible Side Effects continued

Sample Text:

agranulocytosis or neutropenia); sensation of numbness or tingling in fingers and toes (signs of peripheral neuropathy); abdominal pain with nausea, vomiting, or fever (signs of pancreatitis); yellow skin and eyes, nausea, loss of appetite, light-coloured urine (signs of hepatitis); unusual bleeding or bruising (signs of thrombocytopenia); rash, purplish-red spots, fever, itching (signs of inflammation of blood vessels also called vasculitis); swelling mainly of the face and throat (signs of angioedema); rash, skin reddening, blistering of lips, eyes or mouth, skin peeling (signs of erythema multiforme), crushing chest pain (sign of myocardial infarction or increased angina), irregular heart beat (sign of arrhythmia); irregular heart beat (sign of arrhythmia); inflammation of vessels with or without pain (sign of necrotizing vasculitis); rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (signs of toxic epidermal necrolysis); facial rash, joint pain muscle disorder, fever (signs of lupus erythematosus or reactivation of a lupus erythematosus);

Fry Graph



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of syllables per 100 words: **189**
Average # of sentences per 100 words: **0.6**

X = 189

Y = 0.6

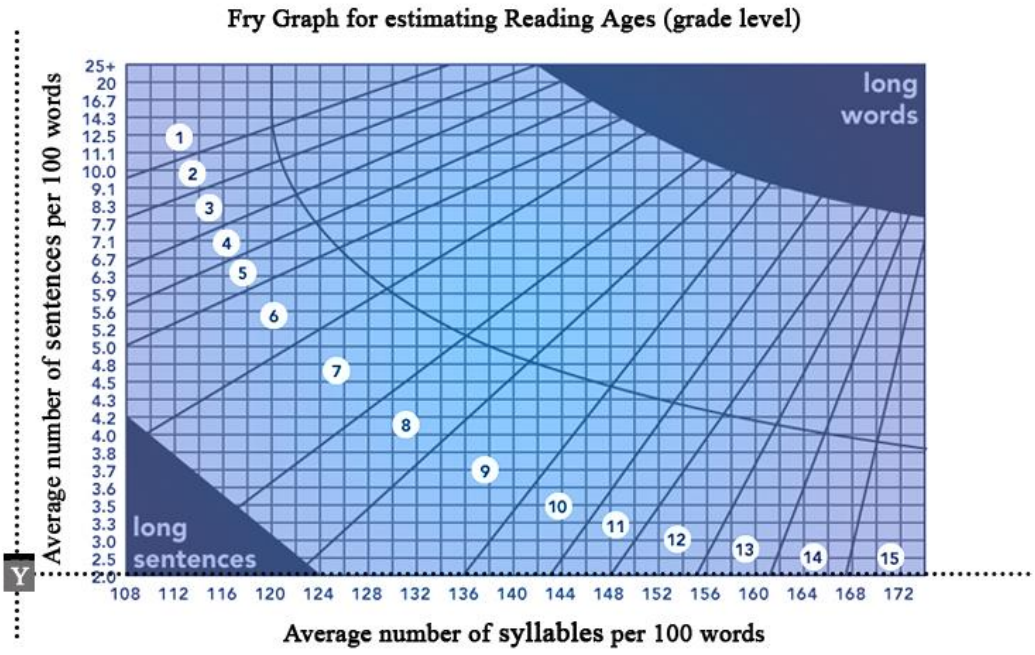
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.4 – Possible Side Effects continued

Sample Text:

weakness, bruising and frequent infections (signs of lack of blood cells also called pancytopenia); pale skin, tiredness, breathlessness, dark urine (signs of low level of red blood cells also called haemolytic anaemia); short and shallow breathing including fever coughing, difficulty breathing, wheezing and breathlessness (signs of respiratory distress, pneumonitis, pulmonary oedema); breathlessness (signs of pulmonary oedema and non cardiogenic pulmonary oedema); rash, purplish-red spots, fever, itching (signs of vasculitis), swelling mainly of the face and throat (signs of angioedema), severely decreased urine output (sign of renal impairment), muscle weakness, muscle spasms, abnormal heart rhythm (signs of hypokalaemia), skin rash with or without itching, together with some of the following signs or symptoms: fever, joint pain, muscle pain, swollen lymph nodes and/or flu-like symptoms (signs of serum sickness), cough with phlegm, chest pain, fever (signs of bronchitis). If any of these affect you severely or if you experience any of these, tell your doctor.

Fry Graph



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of syllables per 100 words: **177**
Average # of sentences per 100 words: **1.3**

X = 177

Y = 1.3

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

APPENDIX 2.2

FRY GRAPHS- COZAAR

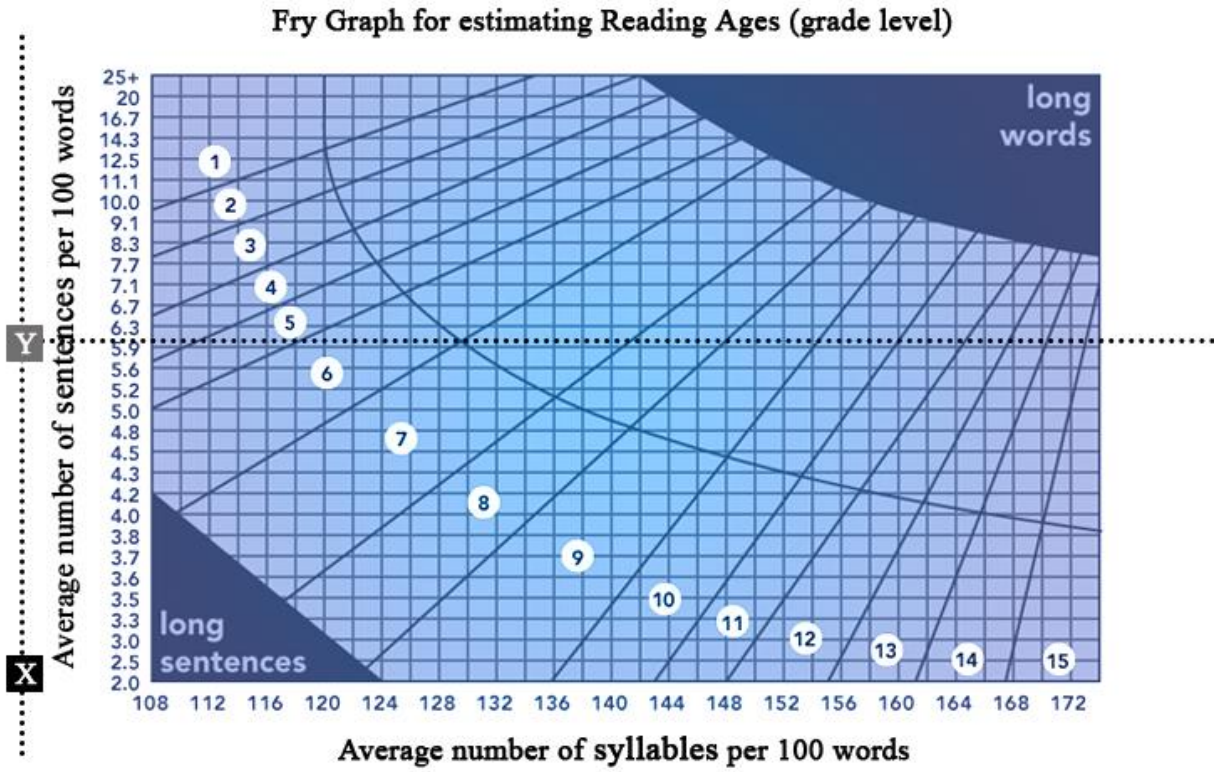
NB: The number between the two parallel lines represents the U.S. grade level.

Section 1- What Cozaar Contains

Sample text:

COZAAR (losartan potassium) is an oval white film- coated tablet which contains 50 mg of losartan potassium as the active ingredient. COZAAR 100 (losartan potassium) is a white film-coated, teardrop-shaped tablet which contains 100 mg of losartan potassium as the active ingredient. In addition, COZAAR and COZAAR 100 contain the following inactive ingredients: Microcrystalline cellulose, Lactose hydrous, Pregelatinised starch, Magnesium stearate, Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose, Titanium dioxide and Carnauba wax. Although COZAAR contains a very small amount of potassium, it cannot replace potassium supplements. If your doctor has prescribed potassium supplements, continue to follow his advice.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

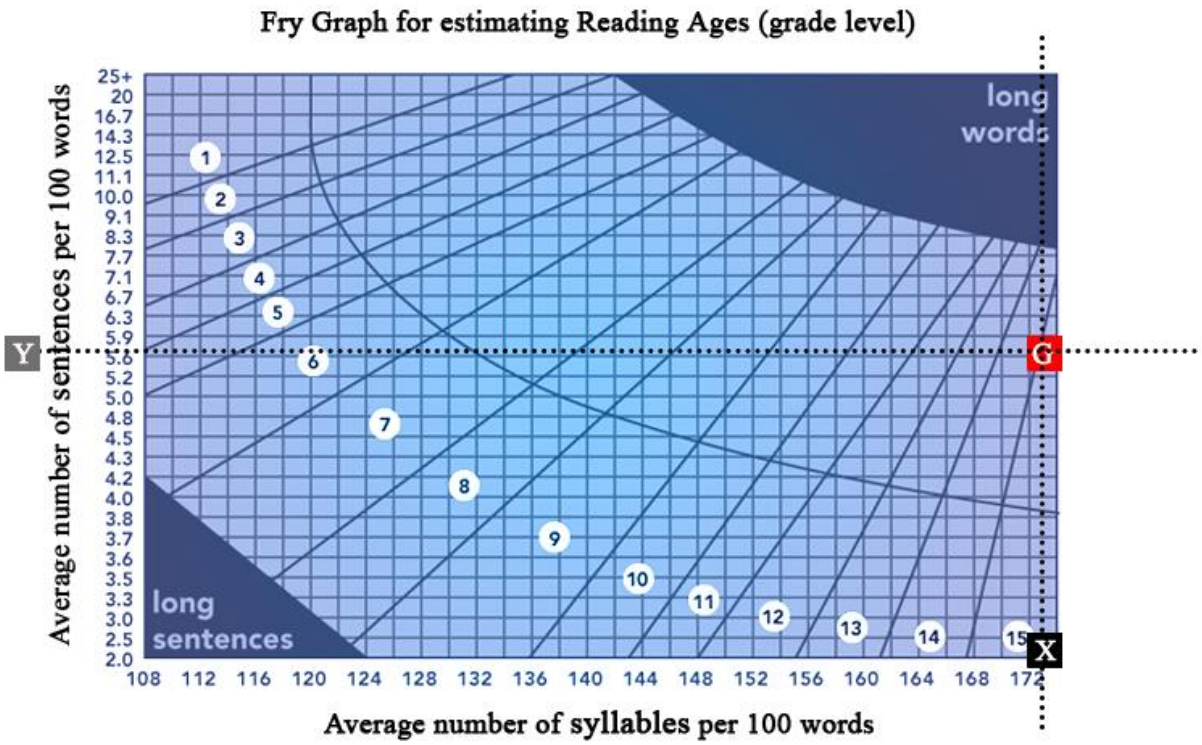
Average # of <u>syllables</u> per 100 words: **207**
Average # of <u>sentences</u> per 100 words: **6**

X = 207
Y = 6
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 2- What Cozaar Is Used For

Sample text:
WHAT COZAAR IS USED FOR: COZAAR is an angiotensin II receptor antagonist which lowers blood pressure. COZAAR also provides kidney protection by delaying the worsening of kidney disease in type 2 diabetic patients with protein in their urine (proteinuria). Kidney disease can be measured by testing the urine for protein. Your doctor has prescribed COZAAR because you have a condition known as hypertension or high blood pressure. Your doctor may also have prescribed COZAAR because you have type 2 diabetes with protein in the urine. In type 2 diabetic patients with protein in the urine, COZAAR has been shown to slow the worsening of kidney disease.

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **172**
Average # of <u>sentences</u> per 100 words: **5.7**

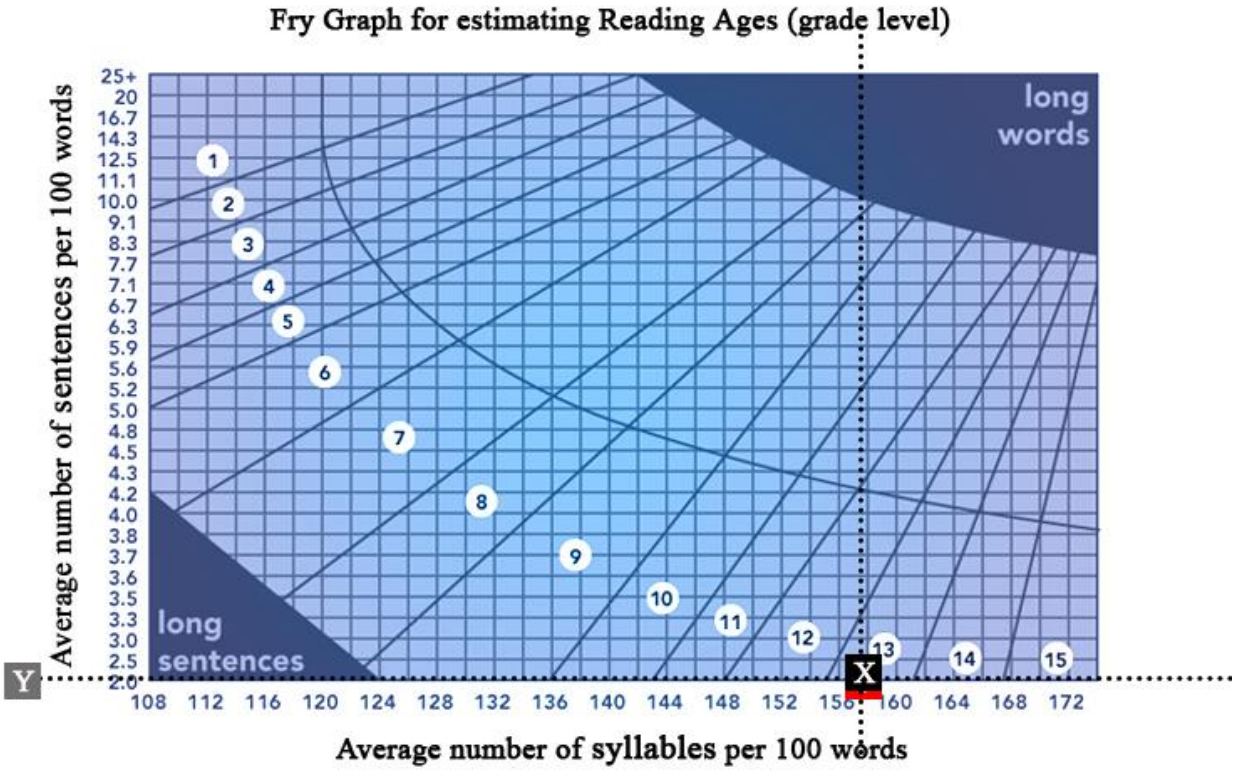
X = 172
Y = 5.7

G= Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.1- Before Taking Cozaar

Sample text:
BEFORE TAKING COZAAR Do not take COZAAR: • if you are allergic to any of its ingredients • if you have had angio-oedema (swelling of the face, lips, mouth, tongue or throat with or without difficulty in swallowing or breathing) while taking an ACE inhibitor or an angiotensin receptor blocker such as COZAAR • if you have aortic stenosis, a narrowing of the aortic valve opening between the left ventricle (large pumping chamber of the heart) and the aorta (the main artery leading away from the heart) • if you have hypertrophic obstructive cardiomyopathy, a heart disorder in which the walls of the ventricles (lower heart chambers) thicken (hypertrophy) and become stiff and the thickened muscle blocks the flow of blood out of the heart • if you have narrowing of the blood vessels to both kidneys or to a single kidney • if you are taking diuretics (water pills) that cause your body to retain potassium such as spironolactone, triamterene and amiloride • if you have severe kidney disease • if you have liver disease • if you are pregnant and breastfeeding (see Pregnancy and Breastfeeding)

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **157**
Average # of <u>sentences</u> per 100 words: **0.5**

X = 157

Y = 0.5

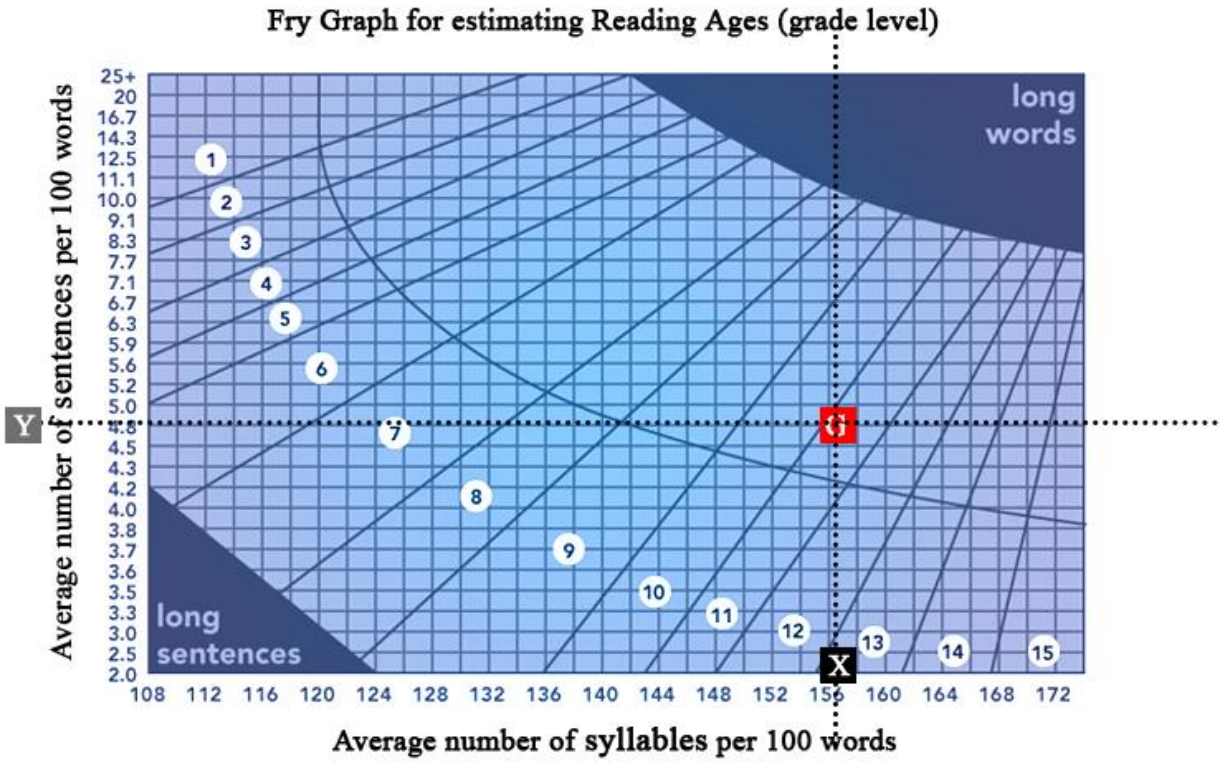
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.2- Before Taking Cozaar continued

Sample text:

Pregnancy and breastfeeding The use of COZAAR while you are pregnant or breastfeeding is contra-indicated. If you are pregnant or become pregnant while taking COZAAR, stop taking COZAAR and talk to your doctor as soon as possible. Take special care with COZAAR: • if you have or have had any medical problems, and any allergies • if you have recently suffered from excessive vomiting or diarrhoea • if you have liver or kidney disease • if you have porphyria Taking COZAAR with food and drink: COZAAR can be taken with or without food. Use in children There is no experience with the use of COZAAR in children. Therefore, COZAAR should not be given to children. Use in elderly COZAAR works equally well in and is equally well tolerated by most older and younger adult patients. Most older patients require the same dose as younger patients.

FRY GRAPH



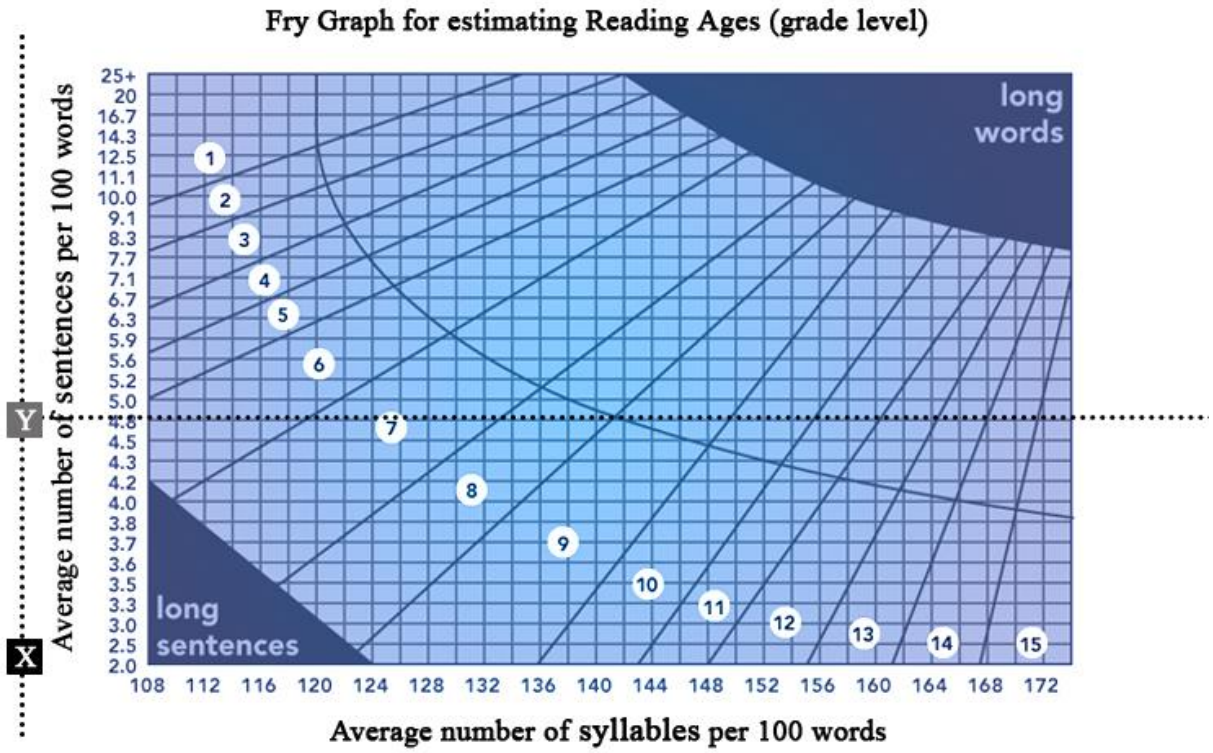
Average # of syllables per 100 words: **156**
Average # of sentences per 100 words: **4.8**

X = 156
Y = 4.8
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.3- Before Taking Cozaar continued

Sample text:
Taking other medicines with COZAAR In general, COZAAR does not interact with food or other medicines you may be taking. You should, however, tell your doctor about all medicines that you are taking or plan to take, including those obtained without a prescription. It is important to tell your doctor if you are taking potassium supplements, potassium-sparing agents or salt substitutes containing potassium. Also tell your doctor if you are taking certain pain and arthritis medicines or lithium (a drug used to treat a certain kind of depression). If you are taking medicines on a regular basis, using the medicine at the same time with another medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

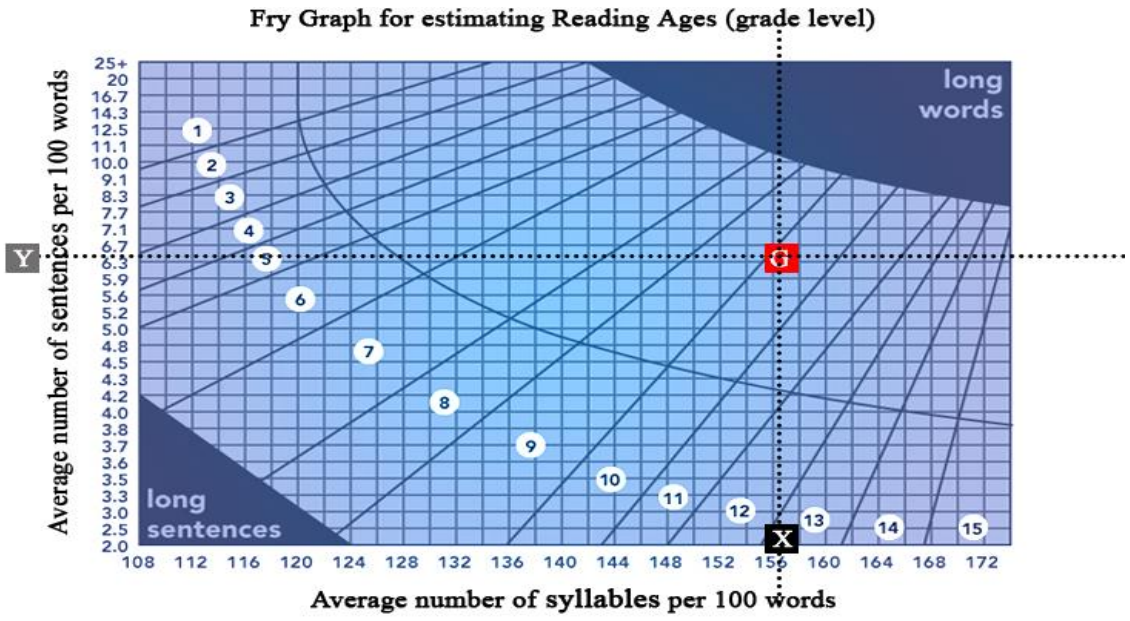
Average # of syllables per 100 words: **181**
Average # of sentences per 100 words: **4.8**

X = 181
Y = 4.8
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 4- HOW TO TAKE COZAAR

Sample text:
HOW TO TAKE COZAAR Take COZAAR every day, exactly as your doctor has instructed. Your doctor will decide on the appropriate dose of COZAAR, depending on your condition and whether you are taking other medicines. It is important to continue taking COZAAR for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure. High blood pressure The usual dose of COZAAR for most patients with high blood pressure is 50 mg taken per day to control blood pressure over the 24-hour period. Type 2 diabetes with protein in the urine The usual dose of COZAAR for most patients is 50 mg taken once a day. The dose may be increased to 100 mg taken once daily. For convenience and to help you remember, try to take COZAAR at the same time each day. Do not share medicines prescribed for you with any other person. If you take more COZAAR than you should: In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre. If you forget to take COZAAR: Try to take COZAAR daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

FRY GRAPH



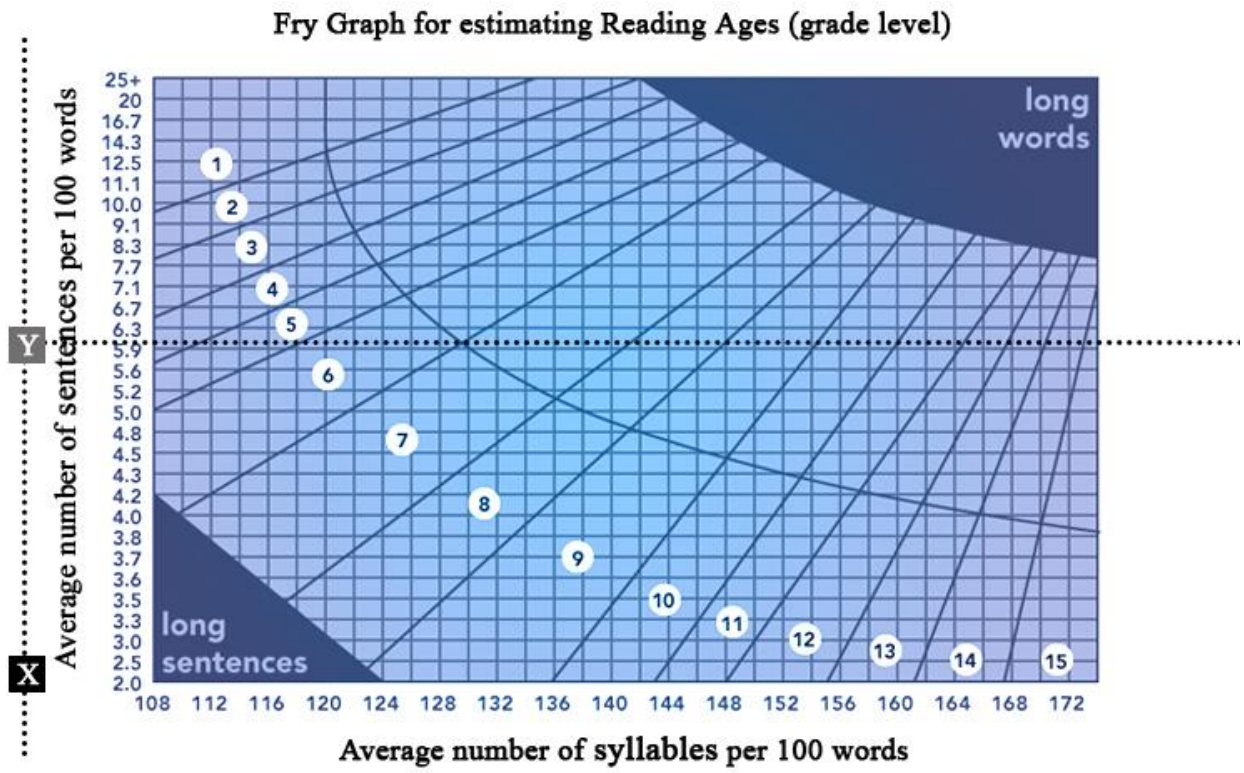
Average # of syllables per 100 words: **156**
Average # of sentences per 100 words: **6.4**

X = 156
Y = 6.4
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.1- SIDE EFFECTS

Sample text:
SIDE EFFECTS What undesirable effects may COZAAR have? Any medicine may have unintended or undesirable effects, so-called side-effects. Some patients may experience dizziness, fatigue, light-headedness, rash or hives, taste alteration, vomiting or increased sensitivity of the skin to sun. Your doctor or pharmacist has a more complete list. Tell your doctor or pharmacist promptly about these or any other unusual symptoms. Some patients, especially those with type 2 diabetes with protein in the urine, may also develop increased levels of potassium in their blood. If you have kidney disease and type 2 diabetes with protein in the urine, and/or are taking potassium supplements, potassium-sparing agents or salt substitutes containing potassium, talk to your doctor.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

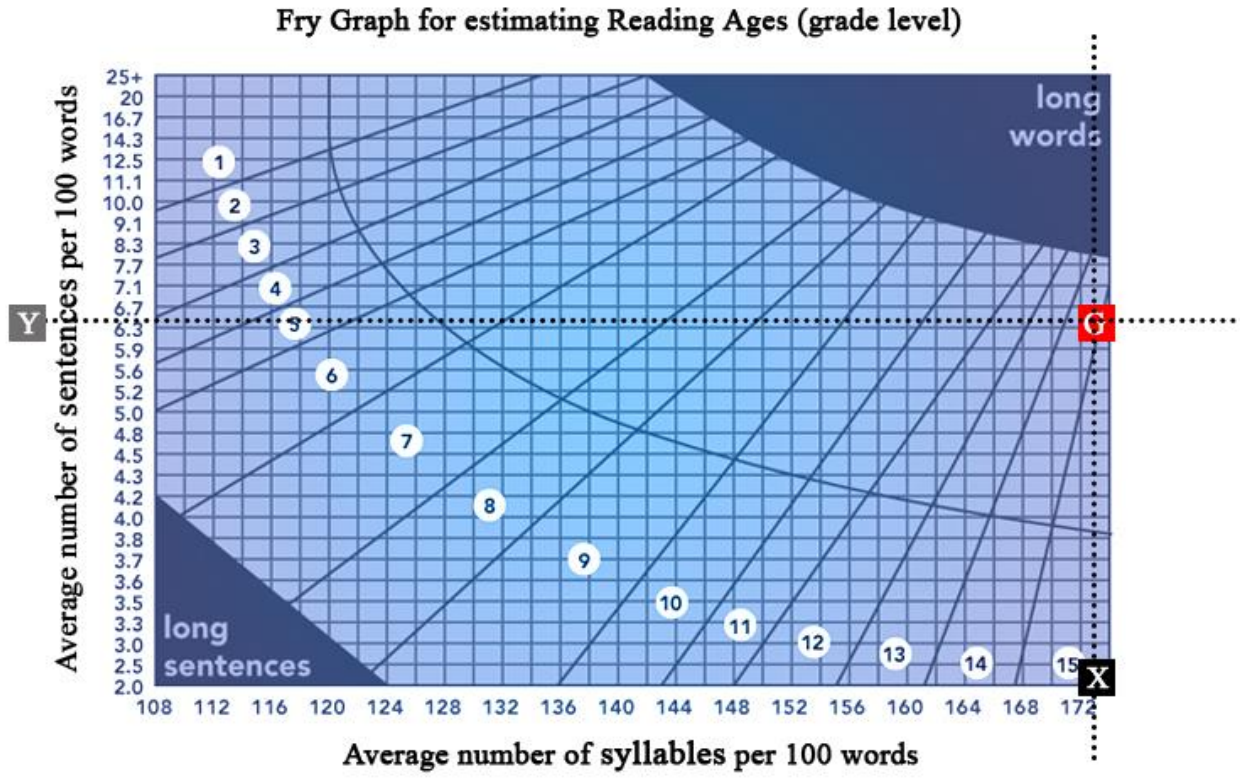
Average # of syllables per 100 words: **182**
Average # of sentences per 100 words: **5.9**

X = 182
Y = 5.9
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.2- SIDE EFFECTS continued

Sample text:
If you develop an allergic reaction involving swelling of the face, lips and/or tongue which may cause difficulty in breathing or swallowing, stop taking COZAAR and contact your doctor immediately. Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice. STORAGE AND DISPOSAL INFORMATION Store COZAAR in a dry place below 30 °C and protect from light. If the temperature rises above 30 °C for an extended period of time, you may store COZAAR in the refrigerator. Keep the container tightly closed. Do not open the blister pack until you are ready to take the medicine. KEEP OUT OF REACH AND SIGHT OF CHILDREN. Do not use this medicine after the month and year following EXPIRES/VERVAL on the carton.

FRY GRAPH



Average # of syllables per 100 words: **172**
Average # of sentences per 100 words: **6.3**


= 172


= 6.3


= Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

APPENDIX 2.3

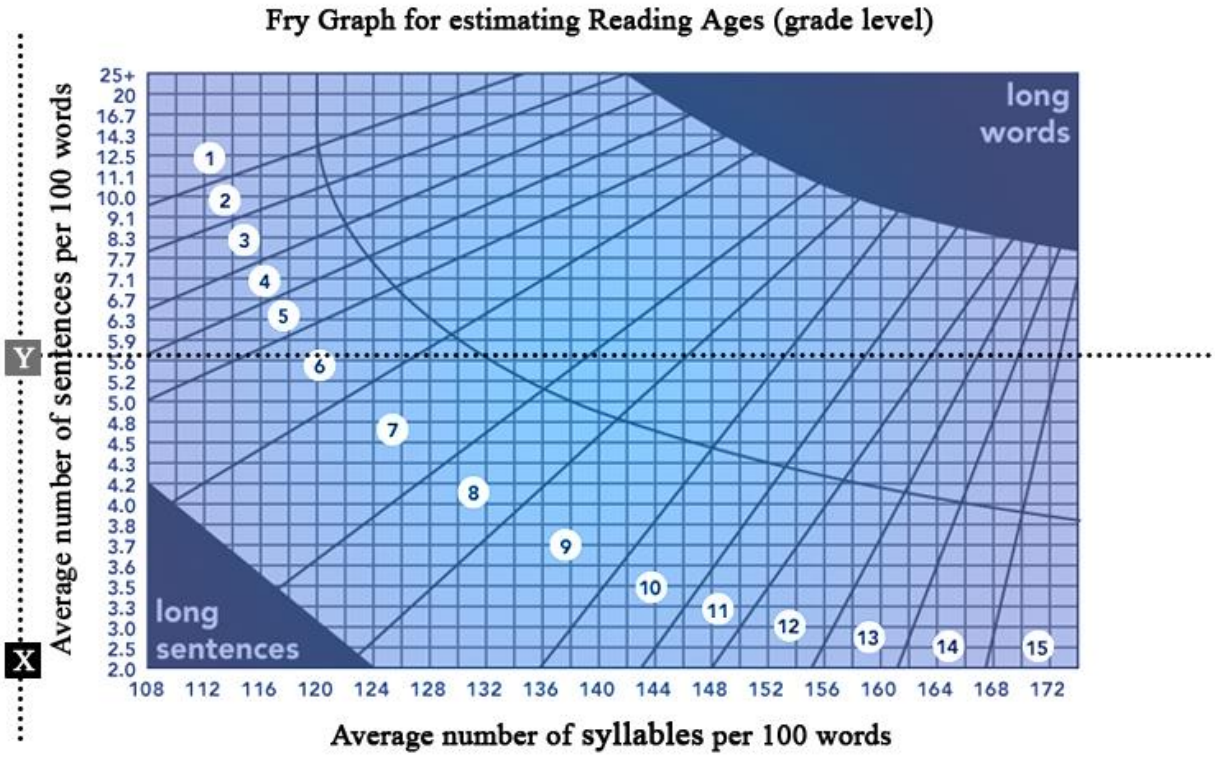
FRY GRAPHS- COZAAR COMP

NB: The number between the two parallel lines represents the U.S. grade level.

Section 1- What Cozaar Comp Contains

Sample text:
WHAT COZAAR COMP CONTAINS COZAAR COMP (losartan potassium-hydrochlorothiazide) are film-coated tablets containing 50 mg of losartan potassium and 12,5 mg of hydrochlorothiazide as the active ingredients. In addition, COZAAR COMP contains the following inactive ingredients: Quinoline yellow aluminium lake, carnauba wax, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose hydrous, magnesium stearate, microcrystalline cellulose, pregelatinised starch, titanium dioxide. COZAAR COMP contains lactose hydrous. Although COZAAR COMP contains a small amount of potassium, it cannot replace potassium supplements. If your doctor has prescribed potassium supplements, continue to follow his advice.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of <u>syllables</u> per 100 words: **227**
Average # of <u>sentences</u> per 100 words: **5.6**

X = 227

Y = 5.6

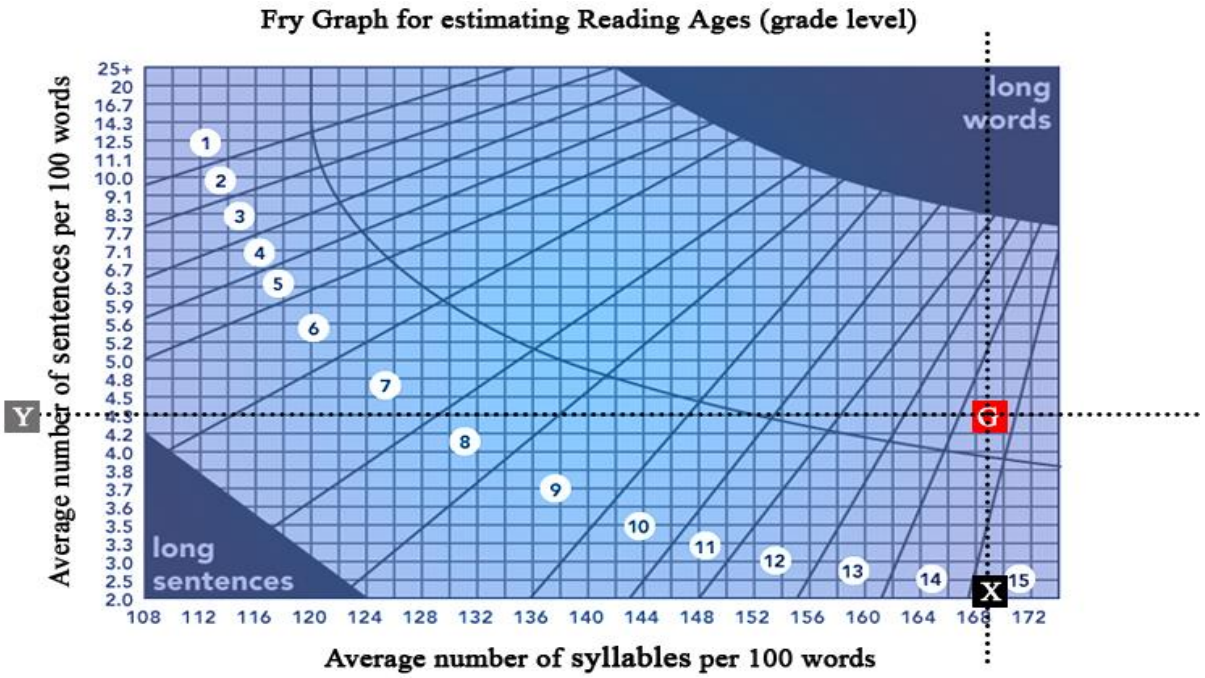
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 2 & 3.1 – What Cozaar Comp Is Used & Before You Take Cozaar Comp

Sample text:

WHAT COZAAR COMP IS USED FOR COZAAR COMP is a combination of angiotensin II receptor antagonist (losartan) and a diuretic (hydrochlorothiazide). Losartan and hydrochlorothiazide work together to lower high blood pressure. Your doctor has prescribed COZAAR COMP because you have a condition known as hypertension or high blood pressure. BEFORE YOU TAKE COZAAR COMP Do not take COZAAR COMP: • If you are allergic to any of its ingredients (see "WHAT COZAAR COMP CONTAINS"). • If you have previously been treated with a medication in the same group of medicines as COZAAR COMP (angiotensin receptor antagonists) or with a medication in the group of medicines known as ACE inhibitors, and have had allergic reactions with swelling of the face, lips, tongue, and/or throat with difficulty in swallowing or breathing. • If you have hereditary or idiopathic angioedema. • If you have hypertrophic obstructive cardiomyopathy, a heart disorder in which the walls of the ventricles (lower heart chambers) thicken (hypertrophy) and become stiff and the thickened muscle blocks the flow of blood out of the heart. • If you have severe kidney disease. • If you have narrowing of the blood vessels to both kidneys or to a single kidney. • If you have aortic stenosis, a narrowing of the aortic valve opening between the left ventricle (large pumping chamber of the heart) and the aorta (the main artery leading away from the heart). • If you are taking diuretics (water pills) that cause your body to retain potassium such as spironolactone, triamterene and amiloride

FRY GRAPH



Average # of syllables per 100 words: **168**
Average # of sentences per 100 words: **4.3**

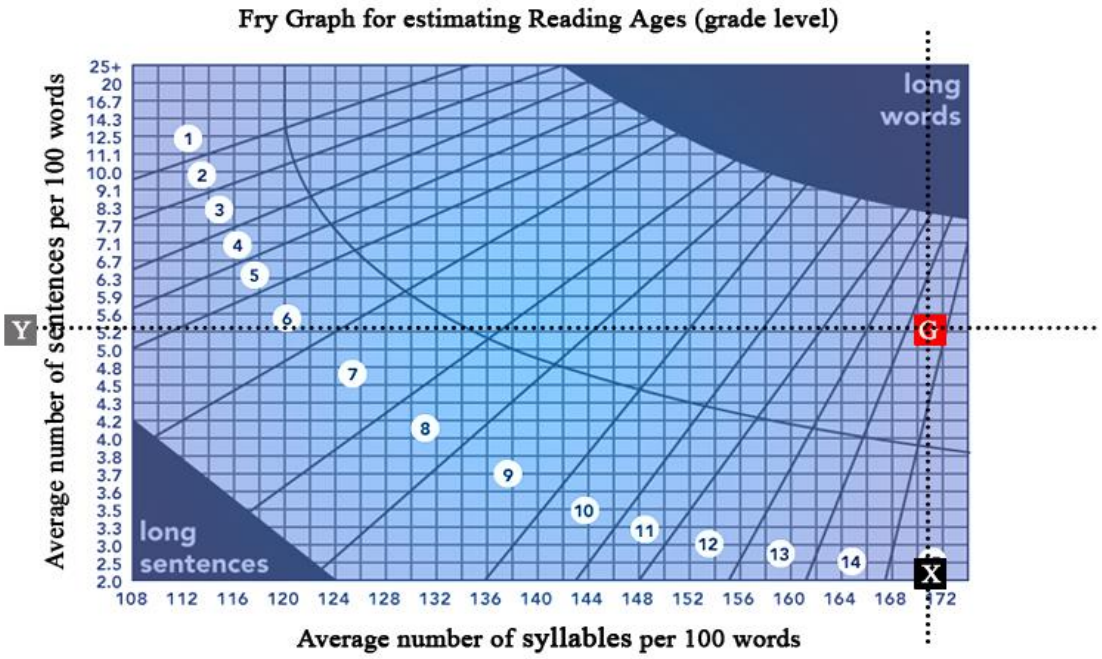
X = 168
Y = 4.3
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.2- Before You Take Cozaar Comp continued

Sample Text:

If you have porphyria. • Thiazide water tablets in (fixed dose) combination with COZAAR COMP should not be given to patients with Addison•s disease. This therapy should also not be used in patients with severe kidney disease or patients not passing urine, and in patients who show allergy to other sulphonamide-derived medicines (ask your doctor if you are not sure what sulphonamide-derived medicines are). • Lithium therapy: Concomitant administration with COZAAR COMP may lead to toxic blood concentrations of lithium. • If you are pregnant or breastfeeding (see •Pregnancy and Breastfeeding•). • If you have liver disease. Take special care with COZAAR COMP If you have or have had medical problems, any allergies, or if you have recently suffered from excessive vomiting or diarrhoea. If you have liver or kidney problems, gout, diabetes, lupus erythematosus, or if you are being treated with diuretics (water tablets). In these cases, your doctor may need to adjust the dose of your medication. Before surgery and anaesthesia (even at the dentist•s office), tell the doctor or dentist that you are taking COZAAR COMP, as there may be a sudden fall in blood pressure associated with the anaesthetic. If you are taking lithium (a medicine used to treat a certain kind of depression).

FRY GRAPH



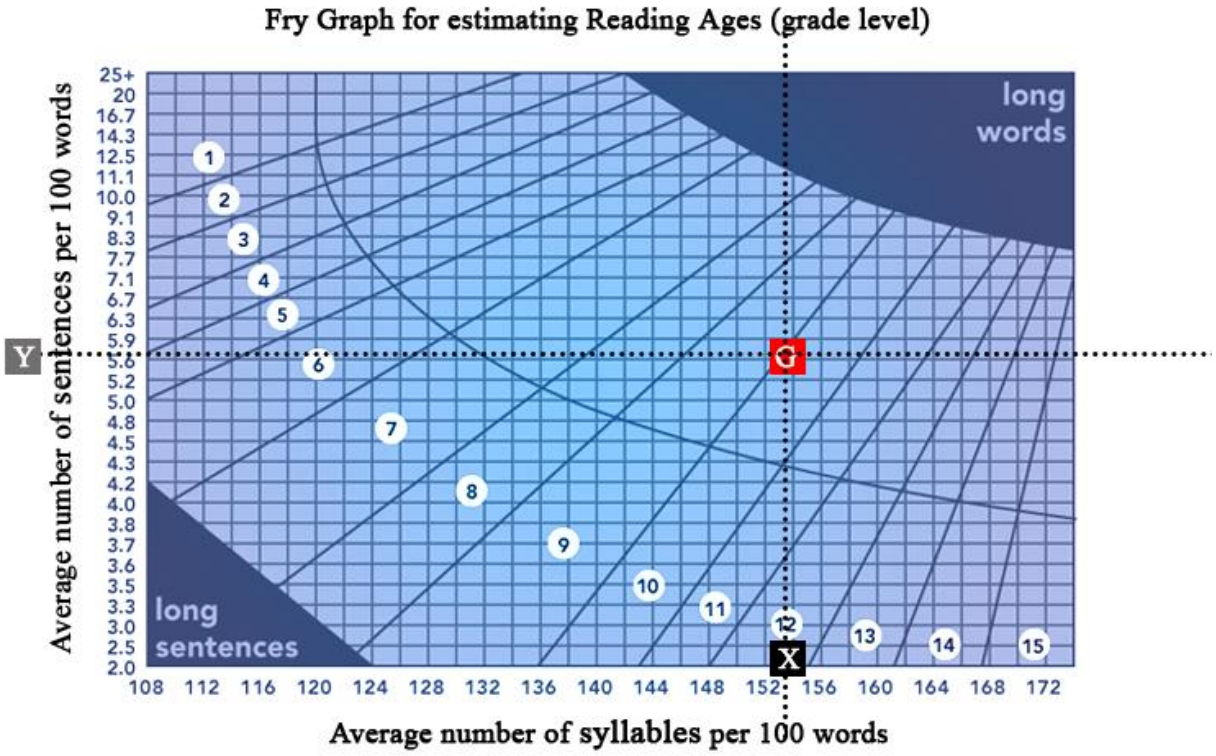
Average # of syllables per 100 words: **170**
Average # of sentences per 100 words: **5.2**

X = 170
Y = 5.2
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.3- Before You Take Cozaar Comp continued

Sample text:
Use in children There is no experience with the use of COZAAR COMP in children. Therefore, COZAAR COMP should not be given to children. Use in the elderly COZAAR COMP works equally well in and is equally well tolerated by most older and younger adult patients. Most older patients require the same dose as younger patients. Taking COZAAR COMP with food and drink COZAAR COMP can be taken with or without food. For convenience and to help you remember, try to take COZAAR COMP at the same time each day. Pregnancy and Breastfeeding The use of COZAAR COMP while you are pregnant or breastfeeding is contra-indicated. If you are pregnant or become pregnant while taking COZAAR COMP, stop taking COZAAR COMP and talk to your doctor as soon as possible. If you are pregnant or breastfeeding your baby while taking COZAAR COMP, please consult your doctor, pharmacist or other healthcare professional for advice.

FRY GRAPH



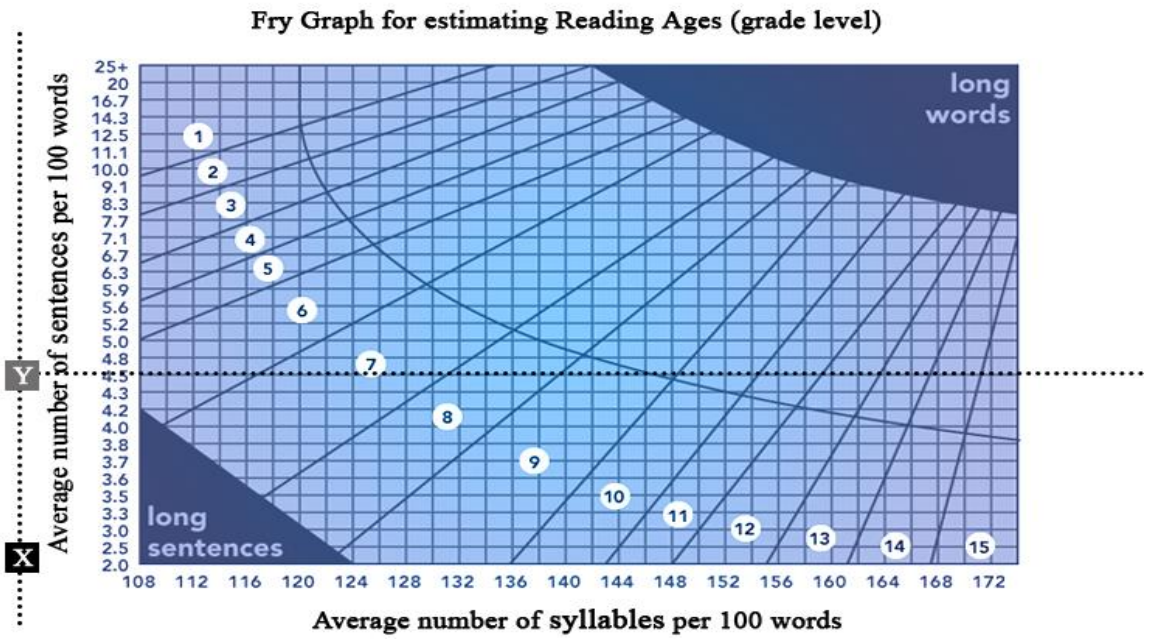
Average # of syllables per 100 words: **153**
Average # of sentences per 100 words: **5.8**

X = 153
Y = 5.8
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.4 - Before You Take Cozaar continued

Sample text:
Driving and using machinery Almost all patients can, but you should not perform tasks which may require special attention (e.g. driving a motorcar or operating dangerous machinery) until you know how you tolerate your medicine. Important information about some of the ingredients of COZAAR COMP COZAAR COMP contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking COZAAR COMP. Taking other medicines with COZAAR COMP In general, COZAAR COMP can be taken with other medicines. You should however, tell your doctor about all medicines that you are taking or plan to take, including those obtained without a prescription. It is especially important for your doctor to know if you are taking other medicines to reduce blood pressure, other diuretics (water tablets), medications to treat diabetes including insulin, resins which reduce high cholesterol, muscle relaxants, pressor amines such as adrenaline, steroids, certain pain and arthritis medicines, or lithium (a medicine used to treat a certain kind of depression). Sedatives, tranquilizers, narcotics, alcohol and analgesics may increase the blood pressure-lowering effect of COZAAR COMP, so tell your doctor if you take any of these medicines. If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of COZAAR COMP with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional for advice.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

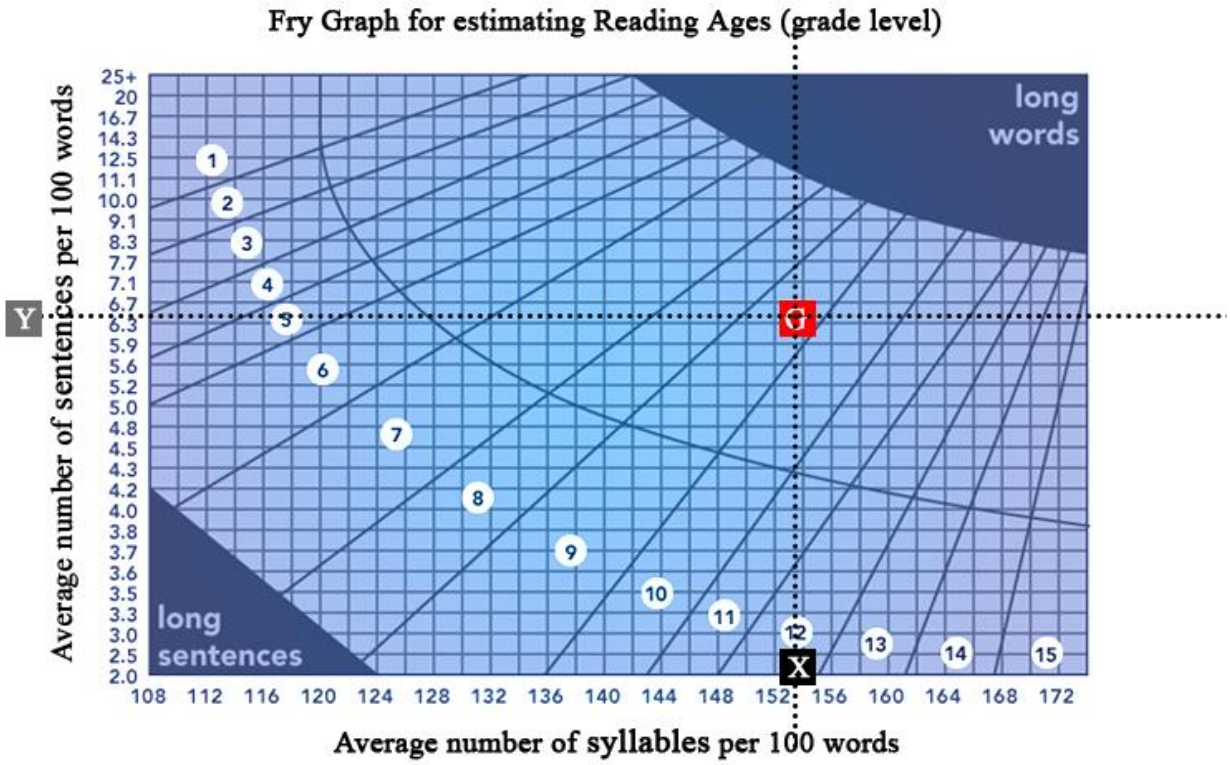
Average # of <u>syllables</u> per 100 words: **187**
Average # of <u>sentences</u> per 100 words: **4.7**

X = 187
Y = 4.7
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 4- How To Take Cozaar Comp

Sample text:
HOW TO TAKE COZAAR COMP: Take COZAAR COMP every day exactly as your doctor has instructed. It is important to continue taking COZAAR COMP for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure. The usual dose of COZAAR COMP for most patients is 1 tablet of COZAAR COMP per day to control blood pressure over the 24 hour period. Do not share medicines prescribed for you with others. If you take more COZAAR COMP than you should In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre. If you forget to take COZAAR COMP Try to take COZAAR COMP daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

FRY GRAPH



Average # of <u>sentences</u> per 100 words: **6.4**

X = 153

Y = 6.4

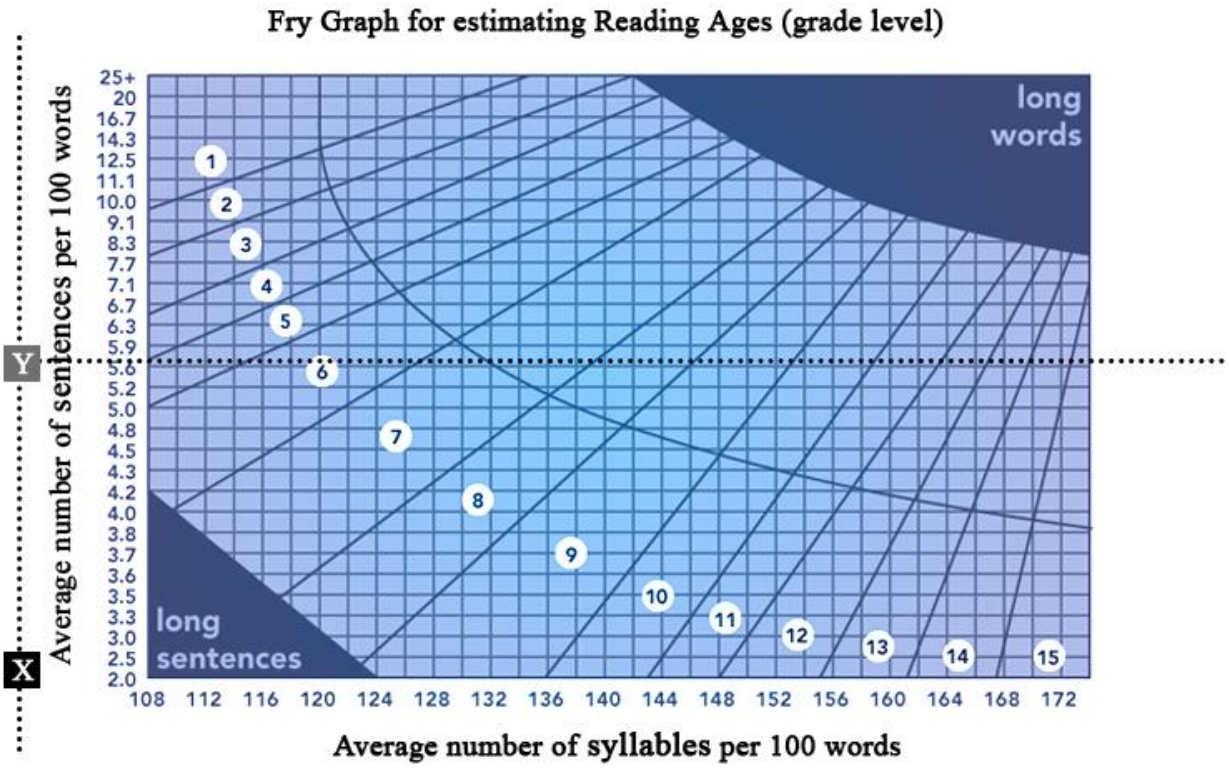
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5- Possible Side Effects

Sample text:

POSSIBLE SIDE EFFECTS: COZAAR COMP can have side effects. Side effects may include nausea, vomiting, cramping, diarrhoea, constipation, headache, weakness, dizziness, fatigue, hives, rash, taste alteration, transient blurred vision or increased sensitivity of the skin to the sun. Another side effect may be a feeling of dizziness or lightheadedness due to a sudden drop in blood pressure when standing up quickly. Your doctor or pharmacist has a more complete list. Tell your doctor or pharmacist promptly about these or any other unusual symptoms. If you develop an allergic reaction involving swelling of the face, lips, throat and/or tongue, stop taking COZAAR COMP immediately and contact your doctor immediately. Not all side effects reported for COZAAR COMP are included in this leaflet. Should your general health worsen while taking COZAAR COMP, please consult your doctor, pharmacist or other healthcare professional for advice.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of <u>syllables</u> per 100 words: **178**
Average # of <u>sentences</u> per 100 words: **5.7**

X = 178

Y = 5.7

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

APPENDIX 2.4

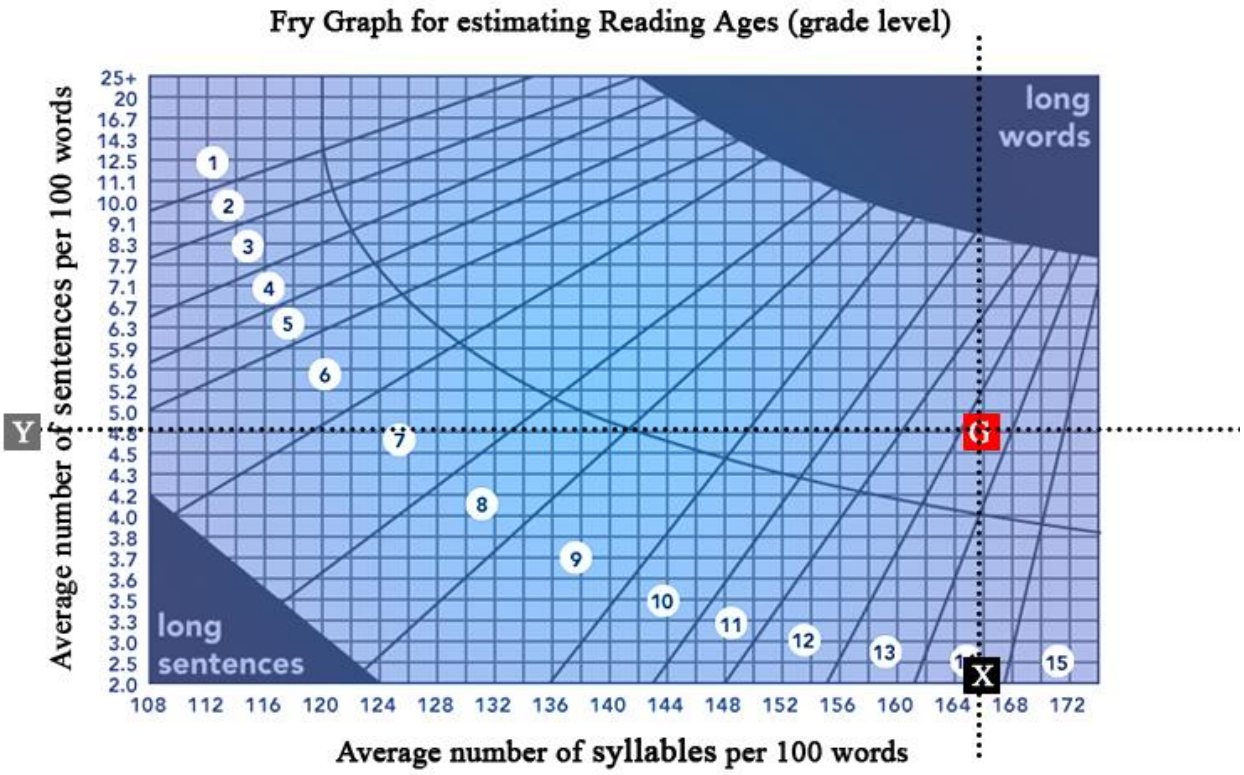
FRY GRAPHS- EXFORGE

NB: The number between the two parallel lines represents the U.S. grade level.

Section 1 & 2- What Exforge Contains & What Exforge Is Used

Sample text:
1. WHAT EXFORGE CONTAINS The active substance of EXFORGE is amlodipine besylate (equivalent to 5 mg or 10 mg amlodipine base) and valsartan (80 mg, 160 mg or 320 mg). The other ingredients are microcrystalline cellulose, sodium starch glycolate (5/320 mg and 10/320 mg), crospovidone, colloidal silica anhydrous, magnesium stearate, hypromellose, polyethylene glycol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E172) (10/160 mg tablets, 5/320 mg and 10/320 mg). 2. WHAT EXFORGE IS USED FOR EXFORGE is used to treat high blood pressure in patients whose blood pressure is not adequately controlled with a single blood pressure lowering medicine.

FRY GRAPH



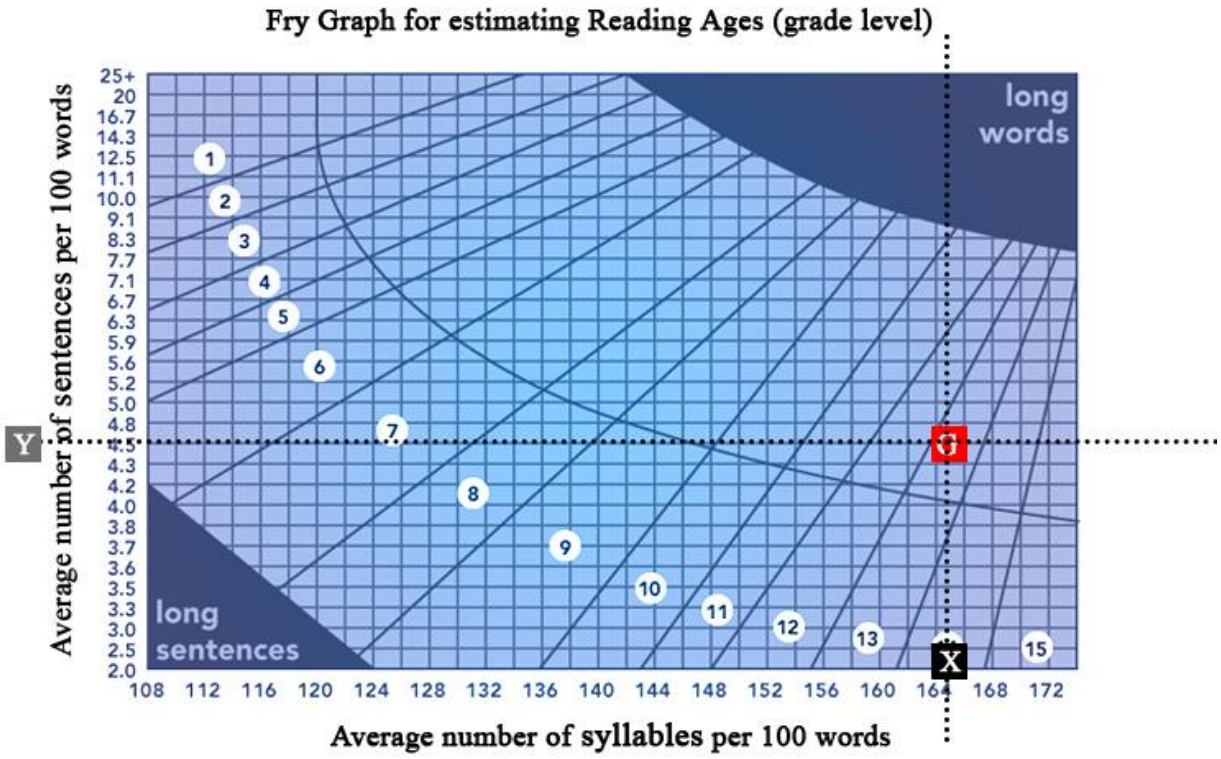
Average # of <u>syllables</u> per 100 words: **165**
Average # of <u>sentences</u> per 100 words: **4.8**

X = 165
Y = 4.8
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.1- Before You Take Exforge

Sample text:
BEFORE YOU TAKE EXFORGE Do not take EXFORGE:
If you have a history of allergies related to taking this type of medicine. If your doctor has diagnosed that you are suffering from a narrowing of valves in your heart (called aortic or mitral stenosis), or abnormally increased thickness of your heart muscle with narrowing (called obstructive hypertrophic cardiomyopathy). If you have received a kidney transplant or if you had been diagnosed to suffer from a narrowing of your kidney artery or if you are suffering from severe kidney problems. If you are taking other medicine or substances, which increase the potassium levels in your blood (such as certain types of diuretics, potassium supplements, etc.). If you are taking medicines that contain lithium (a medicine used to treat some type of depression) If you have ever had an unusual or allergic reaction to amlodipine besylate or valsartan or to any other ingredients of EXFORGE listed at the beginning of this leaflet. If you think you may be allergic, ask your doctor for advice. If you are pregnant or breastfeeding. If any of these apply to you, tell your doctor without taking EXFORGE.

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **164**
Average # of <u>sentences</u> per 100 words: **4.7**

X = 164

Y = 4.7

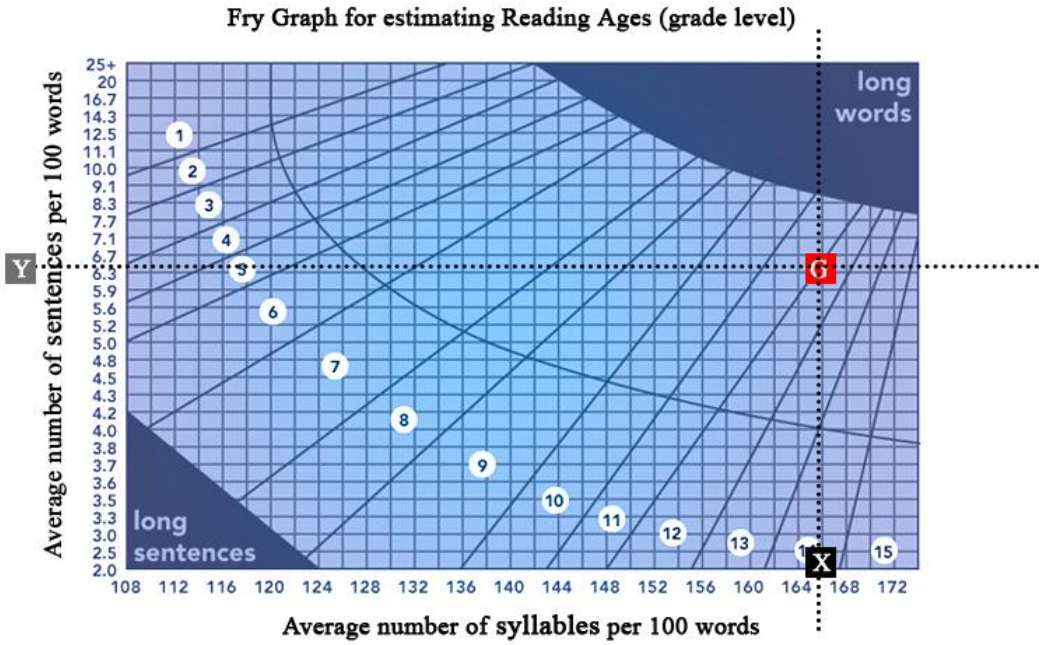
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.2- Before You Take Exforge continued

Sample text:

Take special care with EXFORGE: • If you are suffering from several episodes of vomiting or diarrhoea or are taking a diuretic (a medicine increasing the amount of urine). • If you are taking other medicines or substances, which increase the potassium levels in your blood (such as certain types of diuretics, potassium supplements, etc.). • If you suffer from liver or severe kidney problems. If any of these apply to you, tell your doctor before you take EXFORGE. Taking EXFORGE with food and drink: You can take EXFORGE with or without food. Older people (age 65 years and over): There are no special dose recommendations for patients aged 65 years or older. Children and adolescents (below the age of 18 years): Use of EXFORGE in children and adolescents is not recommended. Pregnancy: Do not take EXFORGE if you are pregnant. Use during pregnancy may cause serious damage to your unborn child. It is therefore important to check with your doctor immediately if you think you may have become pregnant or are planning to become pregnant. Breastfeeding mothers: Tell your doctor if you are breastfeeding. Treatment with EXFORGE is not recommended during breastfeeding.

FRY GRAPH



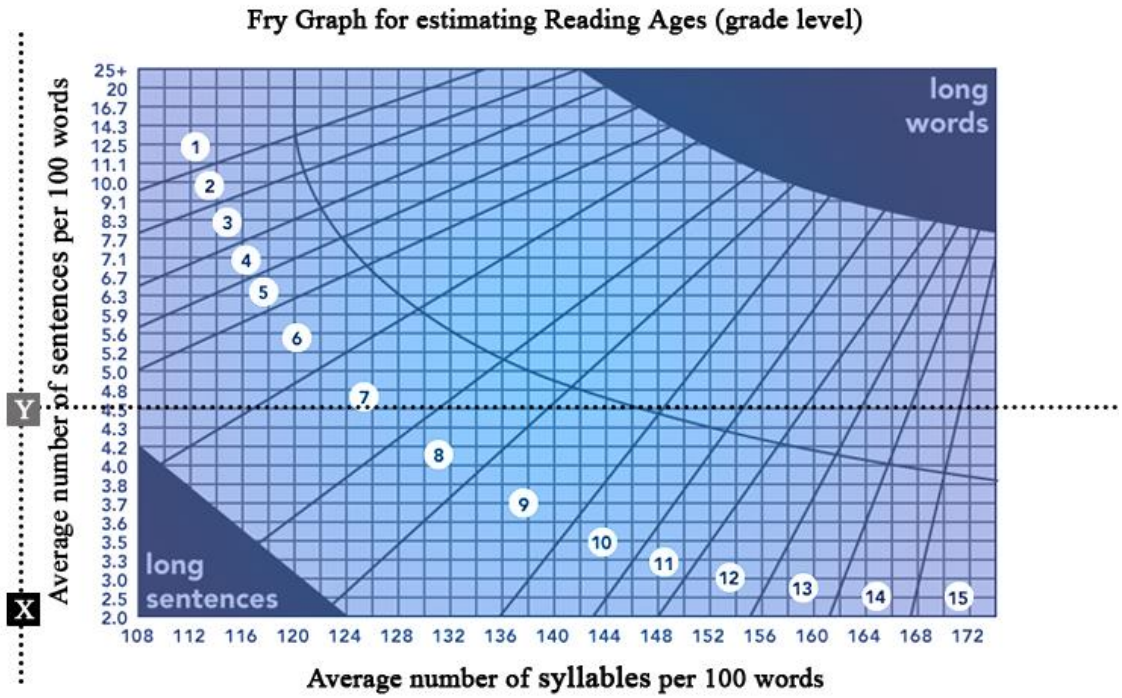
Average # of <u>syllables</u> per 100 words: **165**
Average # of <u>sentences</u> per 100 words: **6.3**

X = 165
Y = 6.3
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.3- Before You Take Exforge continued

Sample text:
Driving and using machines: EXFORGE may cause dizziness and affect the ability to concentrate. So before you drive a vehicle, use machinery, or carry out other activities that require concentration, make sure you know how you react to the effects of EXFORGE. Taking other medicines with EXFORGE: If you are taking other medicines on a regular basis, including complementary or traditional medicines, concomitant use of EXFORGE may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional for advice. It may be necessary to change the dose, to take other precautions, or in some cases to stop taking one of the medicines. This applies to medicines both prescribed and not prescribed by a doctor, especially: • Potassium-sparing medicines, potassium supplements, or salt substitutes containing potassium.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

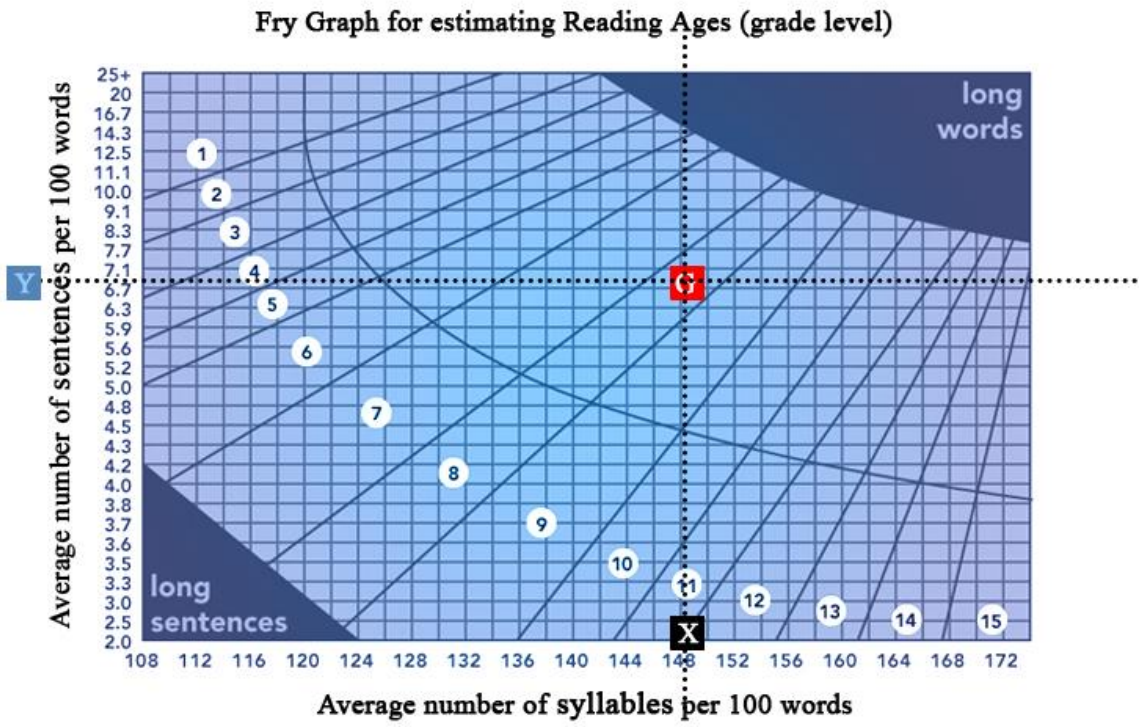
Average # of <u>syllables</u> per 100 words: **198**
Average # of <u>sentences</u> per 100 words: **4.7**

X = 198
Y = 4.7
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 4 - How To Take Exforge

Sample text:
HOW TO TAKE EXFORGE It is very important that you take EXFORGE exactly as your doctor tells you in order to get the best results and reduce the risk of side effects. EXFORGE is for oral use only. Do not exceed the recommended dose. Do not share medicines prescribed for you with others. In the event of overdosage, consult your doctor or pharmacist. If neither is available, rush the patient to the nearest hospital or poison control center. How much EXFORGE to take: Your doctor will tell you exactly how many tablets of EXFORGE you should take. Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose. The recommended dose of EXFORGE is one film coated tablet per day. When and how to take EXFORGE: EXFORGE may be taken with or without food. Swallow the tablets with a glass of water. How long to take EXFORGE: Your doctor will tell you exactly how long you will need to take the tablets. If you take more EXFORGE than you should: If you have accidentally taken too many tablets of EXFORGE, consult your doctor immediately. If you forget to take EXFORGE: It is advisable to take your medicine at the same time each day, preferably in the morning. If you forget to take EXFORGE, take it as soon as you remember and the take your next dose at its usual time. However, if it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for the forgotten tablet. Effects when treatment with EXFORGE is stopped: Stopping your treatment with EXFORGE may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.

FRY GRAPH



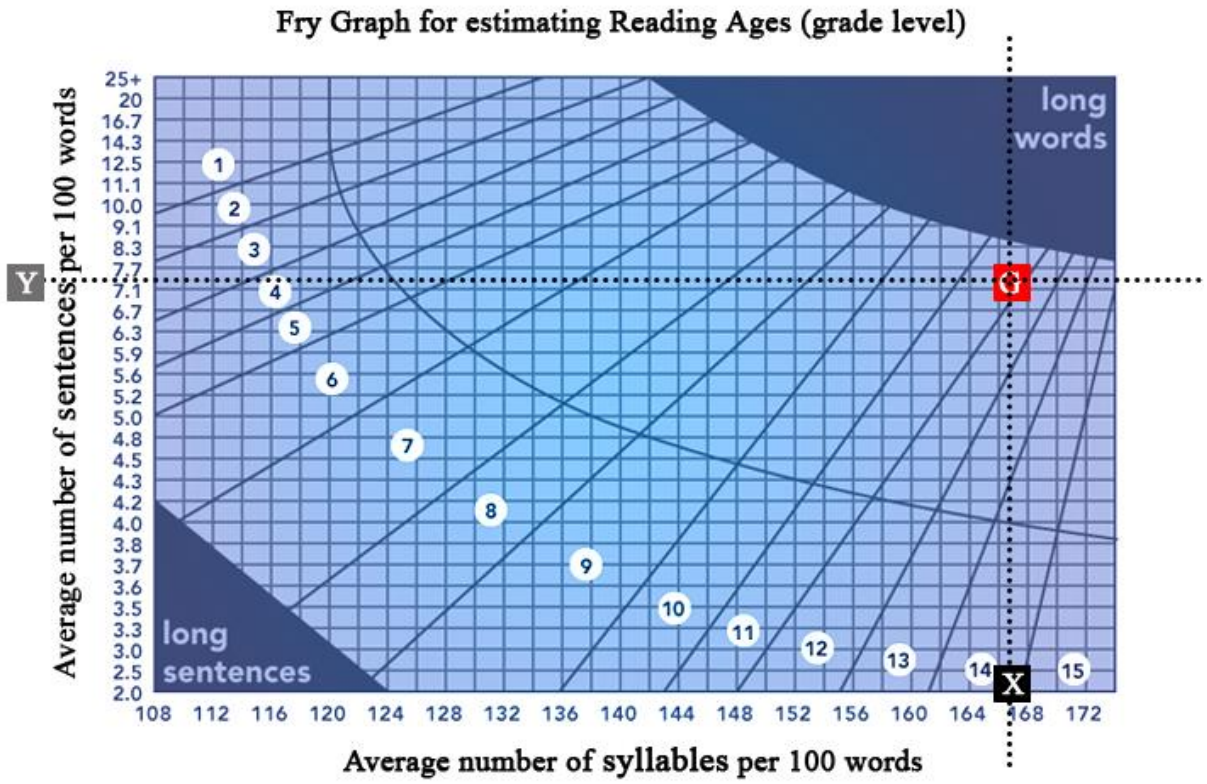
Average # of <u>syllables</u> per 100 words: **148**
Average # of <u>sentences</u> per 100 words: **6.8**

X = 148
Y = 6.8
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.1 - Possible Side Effects

Sample text:
POSSIBLE SIDE EFFECTS EXFORGE can cause unwanted side effects. Not all side effects reported for EXFORGE are included in this leaflet. Should your general health worsen while taking EXFORGE, please consult your doctor, pharmacist or other healthcare professional for advice. EXFORGE can have side effects. Some side effects can be serious. Less frequent: Allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, low blood pressure. If you experience any of these, tell your doctor straight away. Other possible side effects are: Frequent: Flu-like symptoms; nasal congestion, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; redness and warm feeling of the face and/or the neck.

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **166**
Average # of <u>sentences</u> per 100 words: **7.4**

X = 166

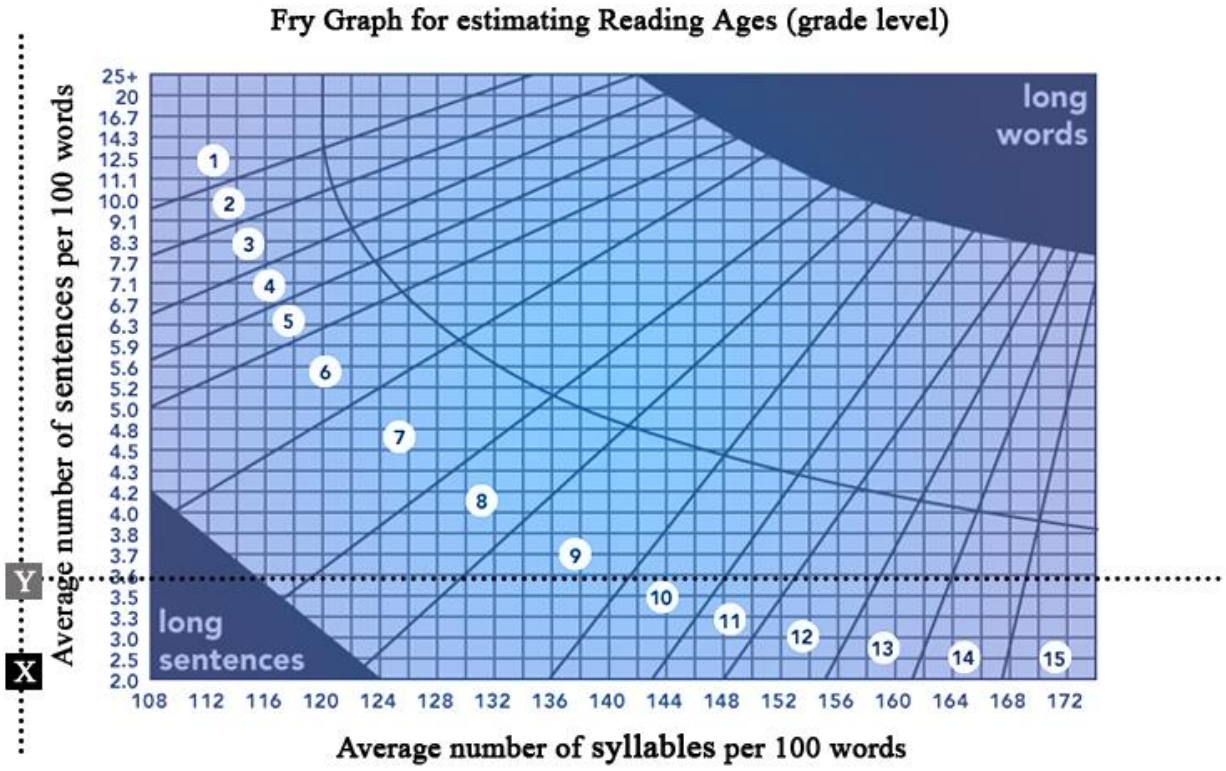
Y = 7.4

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.2- Possible Side Effects continued

Sample text:
Less Frequent: Dizziness; nausea and abdominal pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo; fast heart beat including palpitations; dizziness on standing up; cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints. Anxiety; tinnitus; fainting; passing more urine than normal or feeling an increased urge to pass urine; inability to get or maintain an erection; sensation of heaviness; low blood pressure with symptoms such as dizziness, light-headedness; excessive sweating; generalised skin rash; itching; muscle spasm. If any of these affect you severely, tell your doctor. Additional undesirable effects with amlodipine or valsartan alone, which can be serious, are:

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of <u>syllables</u> per 100 words: **180**
Average # of <u>sentences</u> per 100 words: **3.6**

X = 180

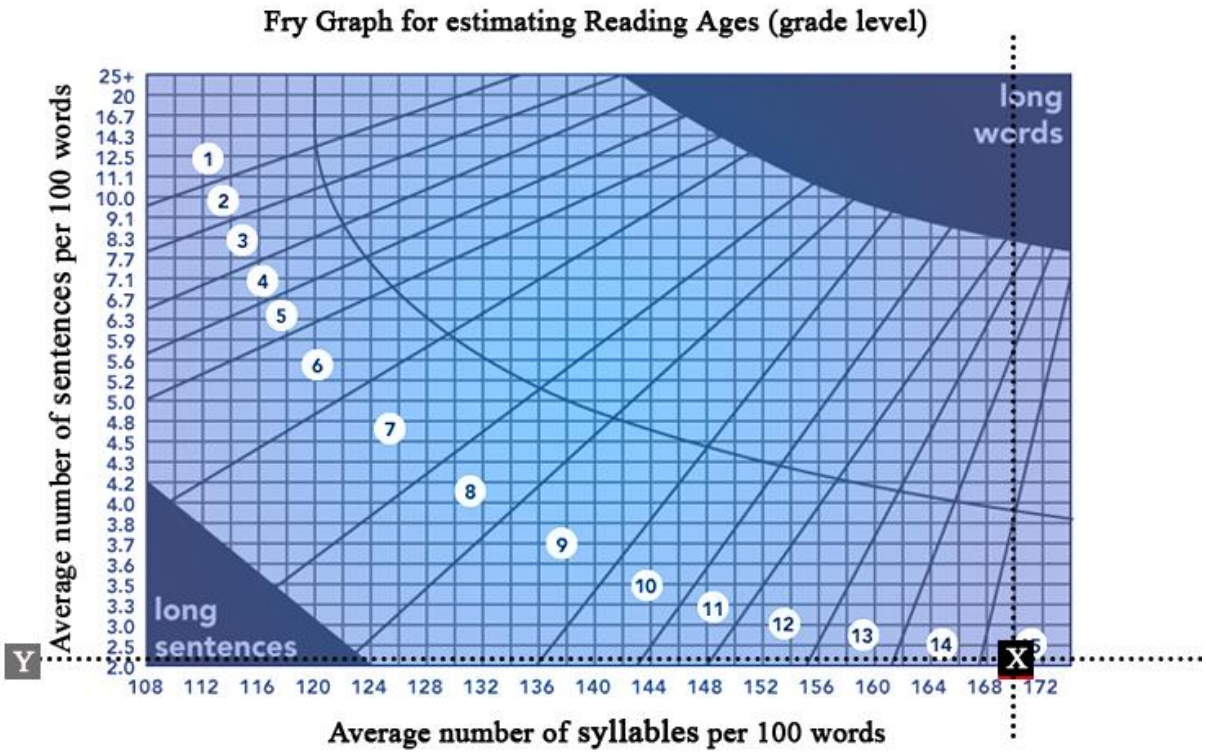
Y = 3.6

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.3 - Possible Side Effects continued

Sample text:
Amlodipine Stomach pain with nausea; thickening of gums; breast enlargement in men; decreased number of white blood cells which could increase the risk of infections; muscle pain; inflammation of the pancreas or liver which can cause symptoms such as vomiting; loss of appetite; nausea; yellow discolouration of the skin and eyes; decreased number of platelets in your blood which could cause bleeding or bruising more easily; inflammation of the blood vessel with skin rash as a symptom; shortness of breath, swelling of the feet or legs due to fluid build-up, easy tiredness after light physical activity (heart disorder), mood changes and depression, altered bowel movements, indigestion, hair loss, rhinitis, increase in blood sugar levels. Valsartan Decreased number of white blood cells which could increase the risk of infections, decreased number of platelets in your blood which could cause bleeding or bruising more easily, insomnia, rhinitis, inflammation of the blood vessel with skin rash as a symptom, decreased sex drive, decrease in neutrophils, increase in potassium levels. If you experience any of these, tell your doctor straight away. If you notice any other effects not mentioned in this leaflet, please inform your doctor or pharmacist.

FRY GRAPH



Average # of syllables per 100 words: **169**
Average # of sentences per 100 words: **2.1**


= 169

= 2.1

= Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

APPENDIX 2.5

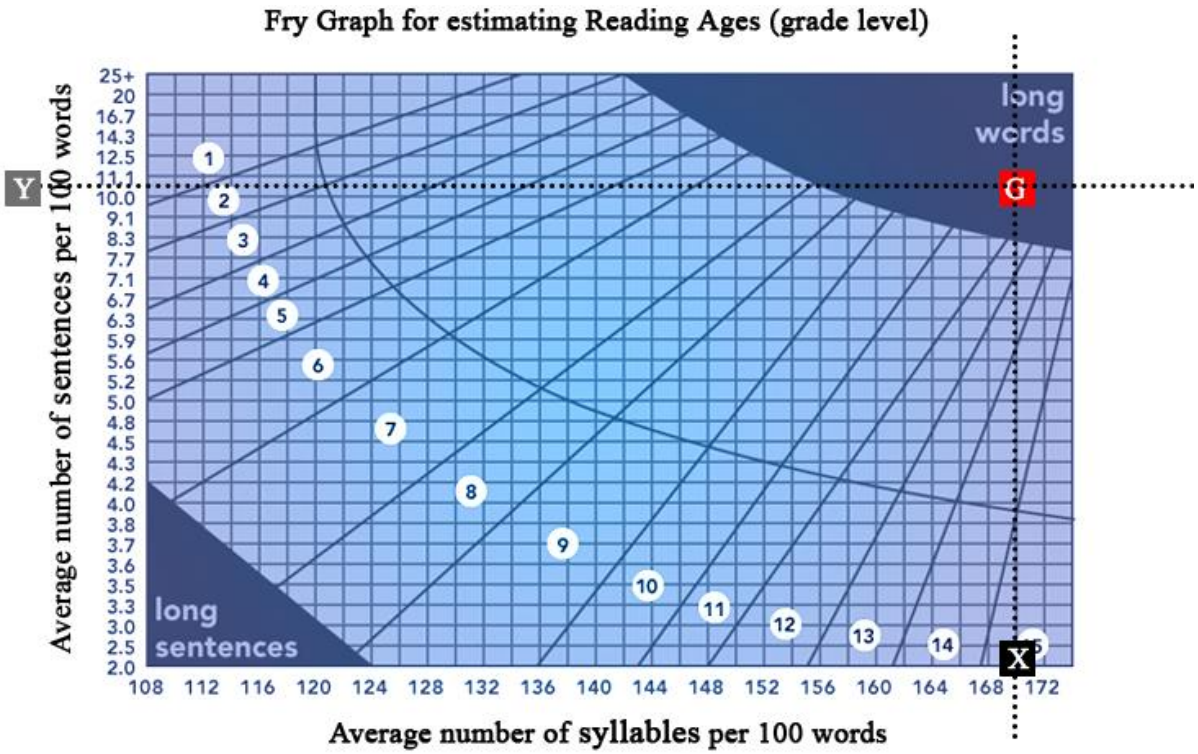
FRY GRAPHS- MICARDIS

NB: The number between the two parallel lines represents the U.S. grade level.

Section 1- What Micardis Tablets Contain

Sample text:
WHAT MICARDIS TABLETS CONTAIN The active ingredient is TELMlSARTAN 40 mg or 80 mg per tablet. The other ingredients are magnesium stearate, meglumine, povidone, sodium hydroxide and sorbitol. 1. WHAT MICARDIS TABLETS CONTAIN The active ingredient is TELMlSARTAN 40 mg or 80 mg per tablet. The other ingredients are magnesium stearate, meglumine, povidone, sodium hydroxide and sorbitol. 1. WHAT MICARDIS TABLETS CONTAIN The active ingredient is TELMlSARTAN 40 mg or 80 mg per tablet. The other ingredients are magnesium stearate, meglumine, povidone, sodium hydroxide and sorbitol. 1. WHAT MICARDIS TABLETS CONTAIN The active ingredient is TELMlSARTAN 40 mg or 80 mg per tablet.

FRY GRAPH



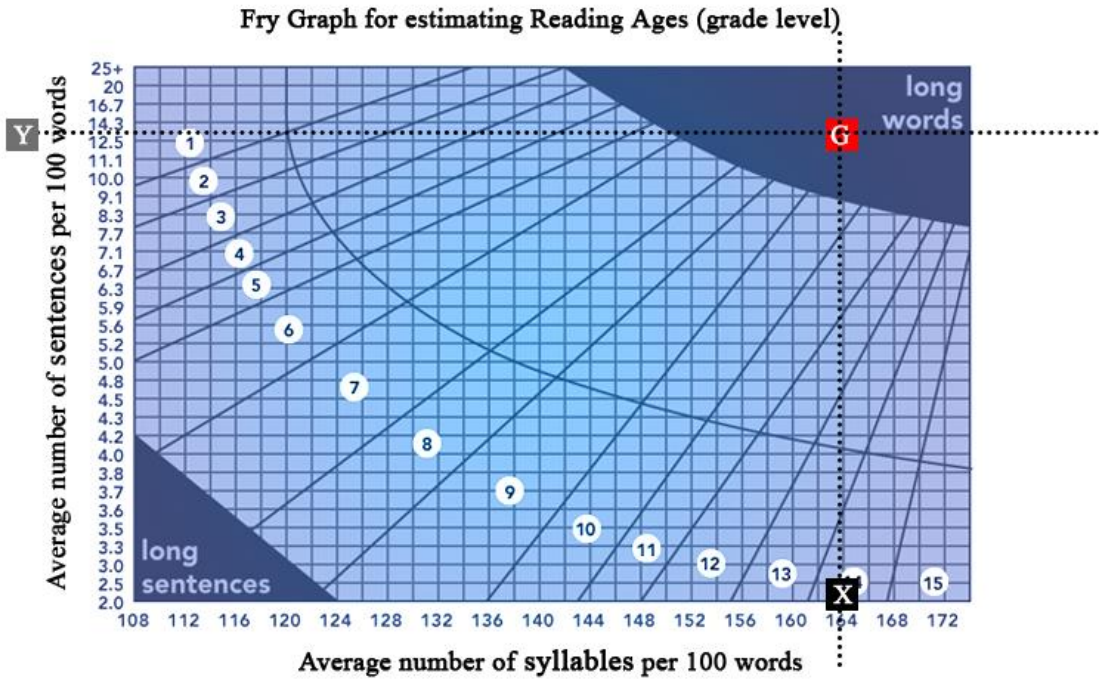
Average # of <u>syllables</u> per 100 words: **169**
Average # of <u>sentences</u> per 100 words: **10.6**

X = 169
Y = 10.6
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 2- WHAT MICARDIS IS USED FOR

Sample text:
WHAT MICARDIS IS USED FOR MICARDIS tablets are used for the treatment of high blood pressure. This is also known as essential hypertension.2. WHAT MICARDIS IS USED FOR MICARDIS tablets are used for the treatment of high blood pressure. This is also known as essential hypertension.2. WHAT MICARDIS IS USED FOR MICARDIS tablets are used for the treatment of high blood pressure. This is also known as essential hypertension.2. WHAT MICARDIS IS USED FOR MICARDIS tablets are used for the treatment of high blood pressure. This is also known as essential hypertension.2. WHAT MICARDIS IS USED FOR MICARDIS tablets are used for the treatment of high blood pressure. This is also known as essential hypertension.

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **163**
Average # of <u>sentences</u> per 100 words: **12.5**

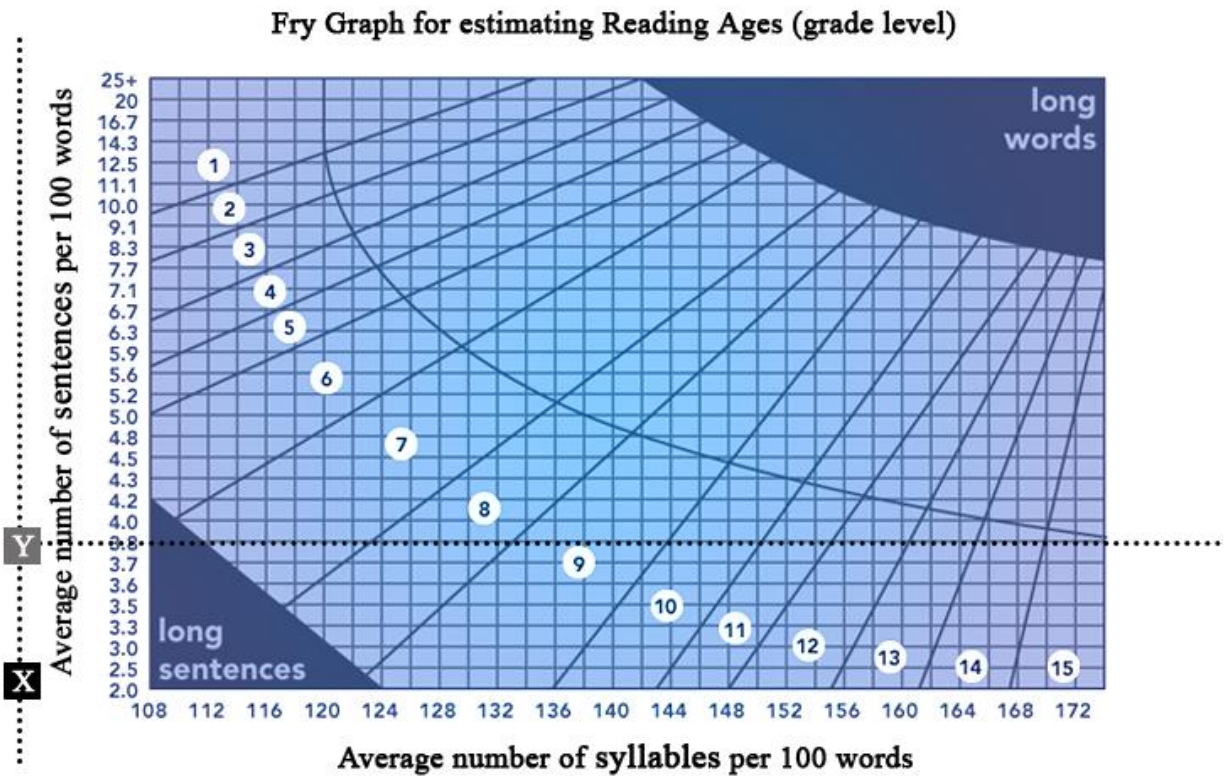
X = 163
Y = 12.5
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.1 - Before You Take Micardis Tablets

Sample Text:

BEFORE YOU TAKE MICARDIS TABLETS Do not take MICARDIS if you are pregnant, are considering becoming pregnant or are breast-feeding. A switch to a suitable alternative treatment should be carried out in advance at planned pregnancy. Do not take MICARDIS if you: • are allergic to telmisartan or any of the other ingredients in the tablets • suffer from the rare hereditary condition called fructose intolerance BEFORE YOU TAKE MICARDIS TABLETS Do not take MICARDIS if you are pregnant, are considering becoming pregnant or are breast-feeding. A switch to a suitable alternative treatment should be carried out in advance at planned pregnancy.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of <u>syllables</u> per 100 words: **178**
Average # of <u>sentences</u> per 100 words: **3.8**

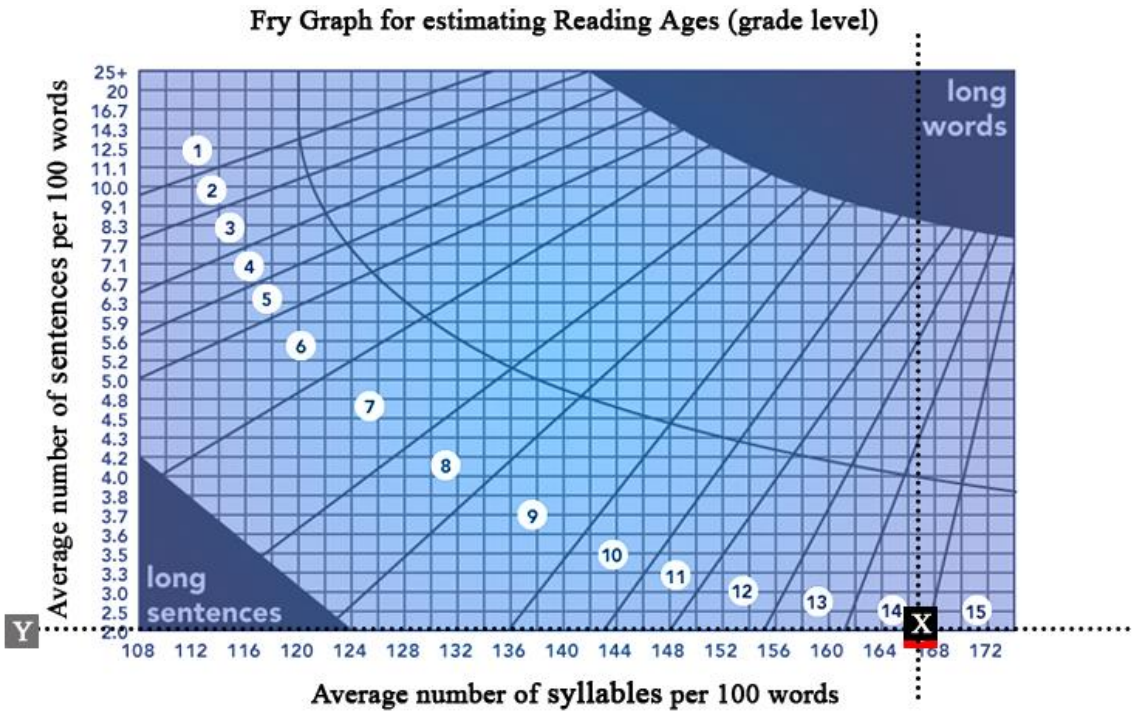
X = 178
Y = 3.8
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.2 - Before You Take Micardis Tablets continued

Sample text:

• have developed swelling of the face, lips, mouth, tongue or throat and giant wheals on your skin when previously taking medicines called angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) • suffer from severe liver disease or biliary obstruction (a problem with the drainage of the bile from the gall bladder) • suffer from obstruction of blood vessels to your heart or kidneys • suffer from porphyria • are currently taking lithium or potassium sparing water tablets containing spironolactone, triamterene or amiloride Take special care with MICARDIS and tell your doctor if you: • suffer from kidney disease or have had a kidney transplant • suffer from liver problems • have heart problems • if your body could be lacking in salt due to a low salt diet, or if you have recently lost a lot of body fluids due to taking strong diuretic medicines (water tablets), vomiting or diarrhoea • have high potassium levels in your blood or use salt substitutes containing potassium • have been told previously that you have raised aldosterone levels • are already taking a medicine called an angiotensin converting enzyme inhibitor (ACE-I)

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **166**
Average # of <u>sentences</u> per 100 words: **0.5**

X = 166

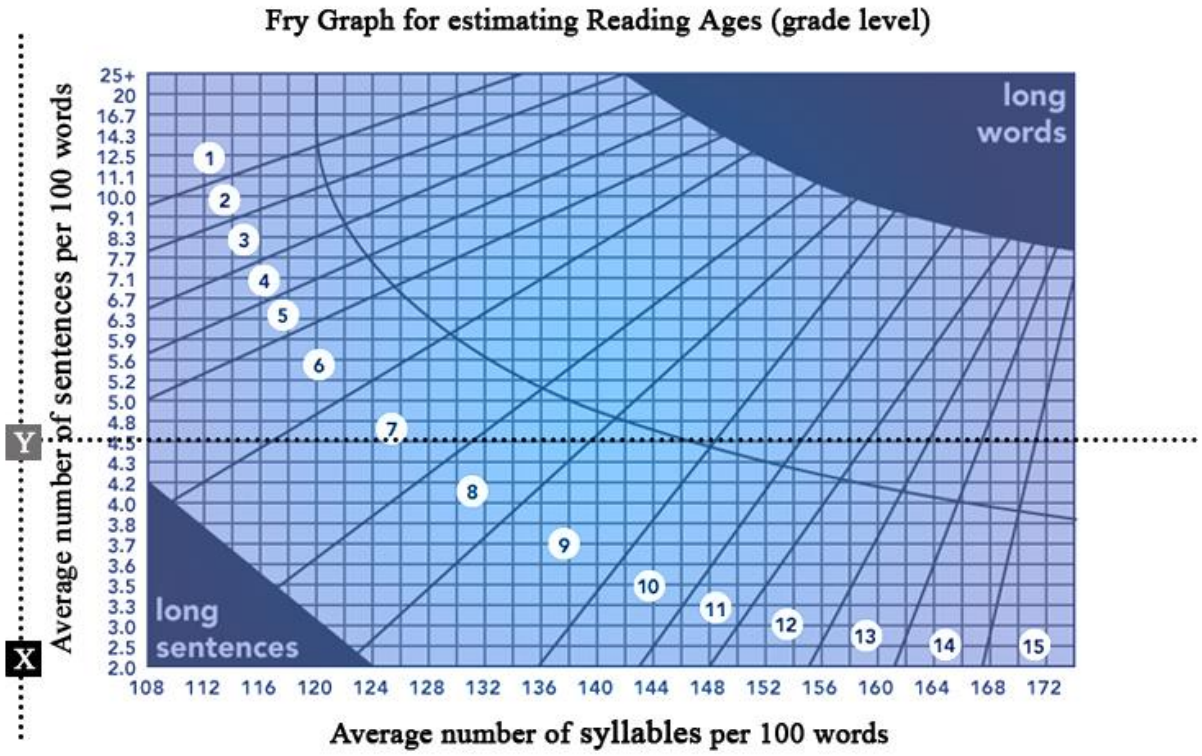
Y = 0.5

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.3- Before You Take Micardis Tablets continued

Sample text:
Pregnancy and breast-feeding: Do not take MICARDIS if you are pregnant, are considering becoming pregnant or are breast-feeding. A switch to a suitable alternative treatment should be carried out in advance of planned pregnancy. Driving and using machinery: When driving vehicles or operating machinery, it should be taken into account that dizziness or drowsiness may occasionally occur when taking blood pressure lowering medication. Important information about some of the ingredients of MICARDIS: Sorbitol is not suitable for patients with hereditary fructose intolerance. Taking other medicines with MICARDIS: If you are taking other medicines on a regular basis, including medicines bought over the counter and complementary or traditional medicines, the use of MICARDIS with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice. MICARDIS can interfere with some other medicines such as digoxin, lithium, ACE-inhibitors and non-steroidal anti-inflammatory medicines (NSAIDs) like aspirin.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of <u>syllables</u> per 100 words: **204**
Average # of <u>sentences</u> per 100 words: **4.5**

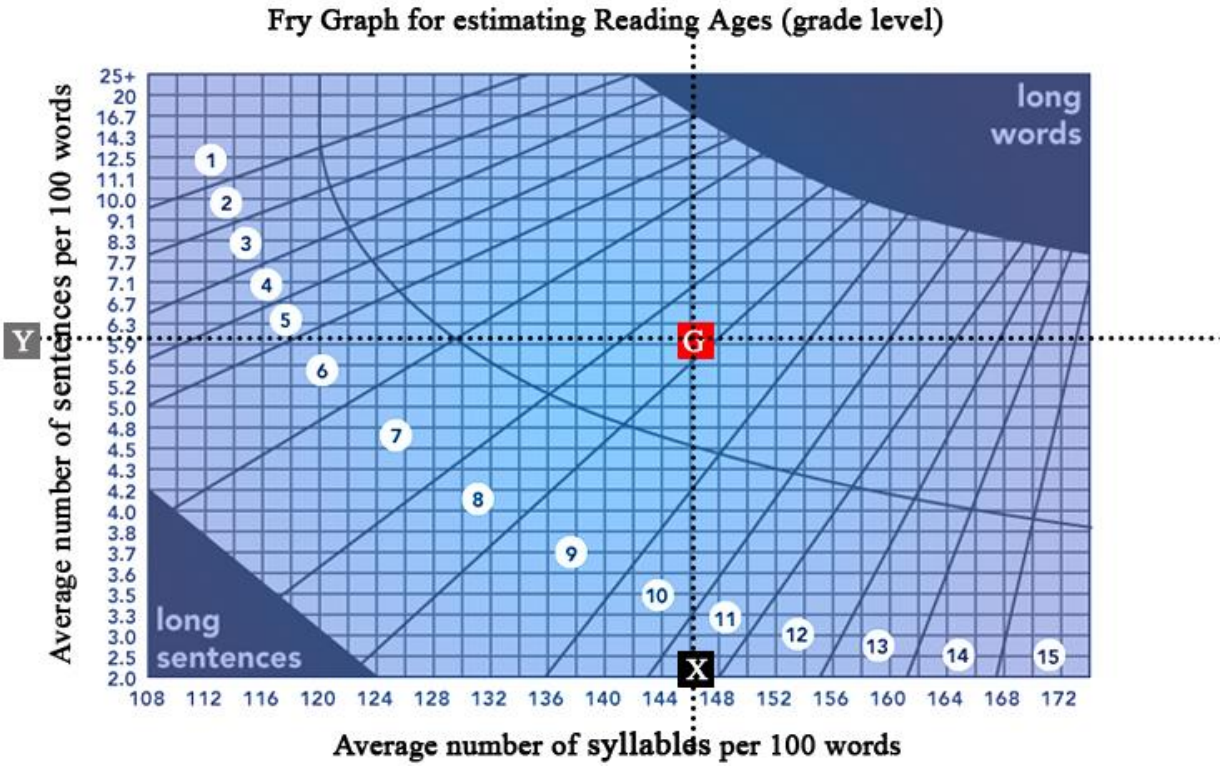
X = 204
Y = 4.5

G= Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 4- How To Take Micardis

Sample text:
HOW TO TAKE MICARDIS • Take MICARDIS tablets exactly as your doctor has instructed you. Do not take more or less tablets and do not take them more often than recommended. You should check with your doctor or pharmacist if you are unsure. • If you have the impression that MICARDIS is too strong or too weak, talk to your doctor or pharmacist. • MICARDIS tablets are only for adults and should not be taken by children and adolescents up to 18 years. MICARDIS is usually taken in a dose of one 40 mg or 80 mg tablet once daily (preferably at about the same time each day) and swallowed with a drink of water. Your doctor may prescribe MICARDIS in combination with other blood pressure lowering medicines.

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **146**
Average # of <u>sentences</u> per 100 words: **6.2**

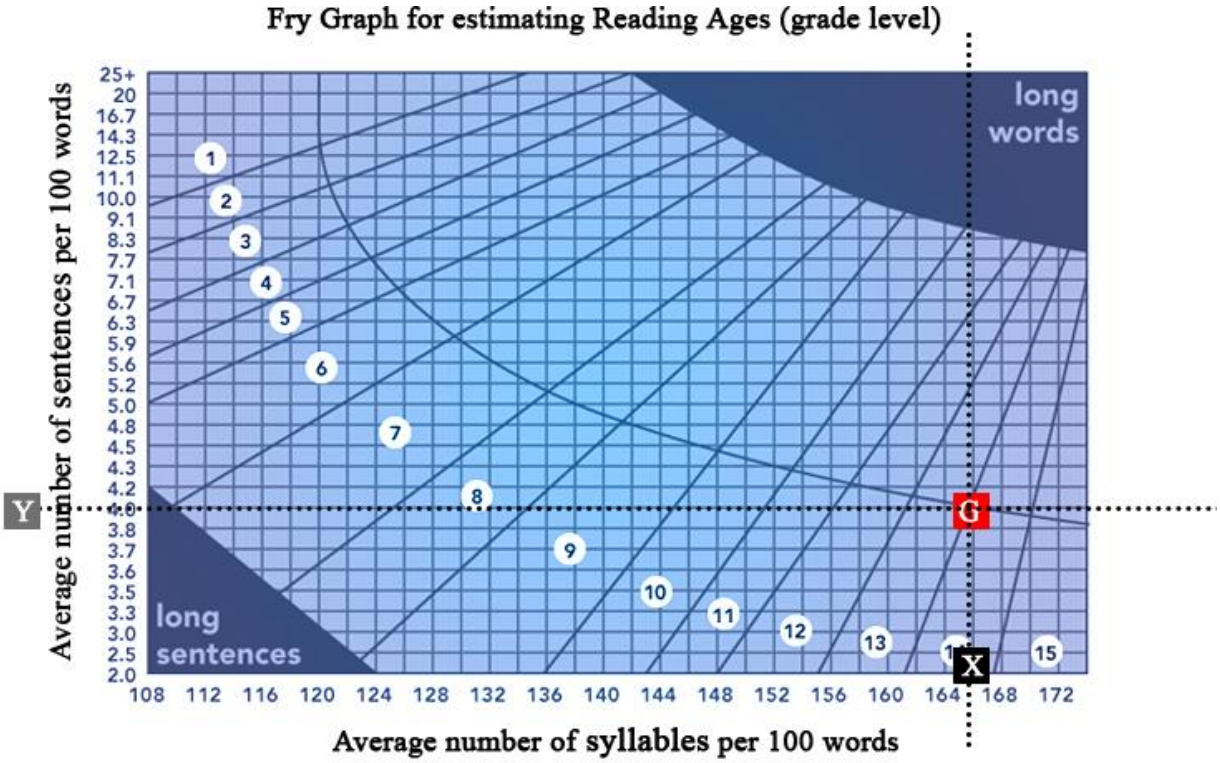
X= 146
Y= 6.2

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.1 - Possible Side-Effects

Sample text:
If you take more MICARDIS than you should: In the event of overdosage or accidental intake, consult your doctor or pharmacist. If neither is available, seek help at the nearest hospital or poison control centre. If you forget to take MICARDIS: If you miss a dose of this medicine, take it as soon as you remember on the same day. If you do not take your tablet on that same day, take your normal dose on the next day. Do not double the dose to make up for forgotten individual doses. 5. POSSIBLE SIDE-EFFECTS MICARDIS tablets can have side-effects. The following side-effects have been reported uncommonly (affecting less than 1 in 100 patients): • urinary tract infections (including inflammation of the bladder), upper respiratory tract infections • anaemia and other changes to the blood chemistry • elevated blood potassium levels • depression, difficulty sleeping • faintness, dizziness for example when standing up quickly • changes in the heart-rate, low blood pressure, shortness of breath • abdominal pain, loose/runny stools, indigestion, flatulence, vomiting • increased sweating, skin rashes and itching • back pain, muscle tenderness, cramps in the legs, chest pain, weakness • impaired kidney function

FRY GRAPH



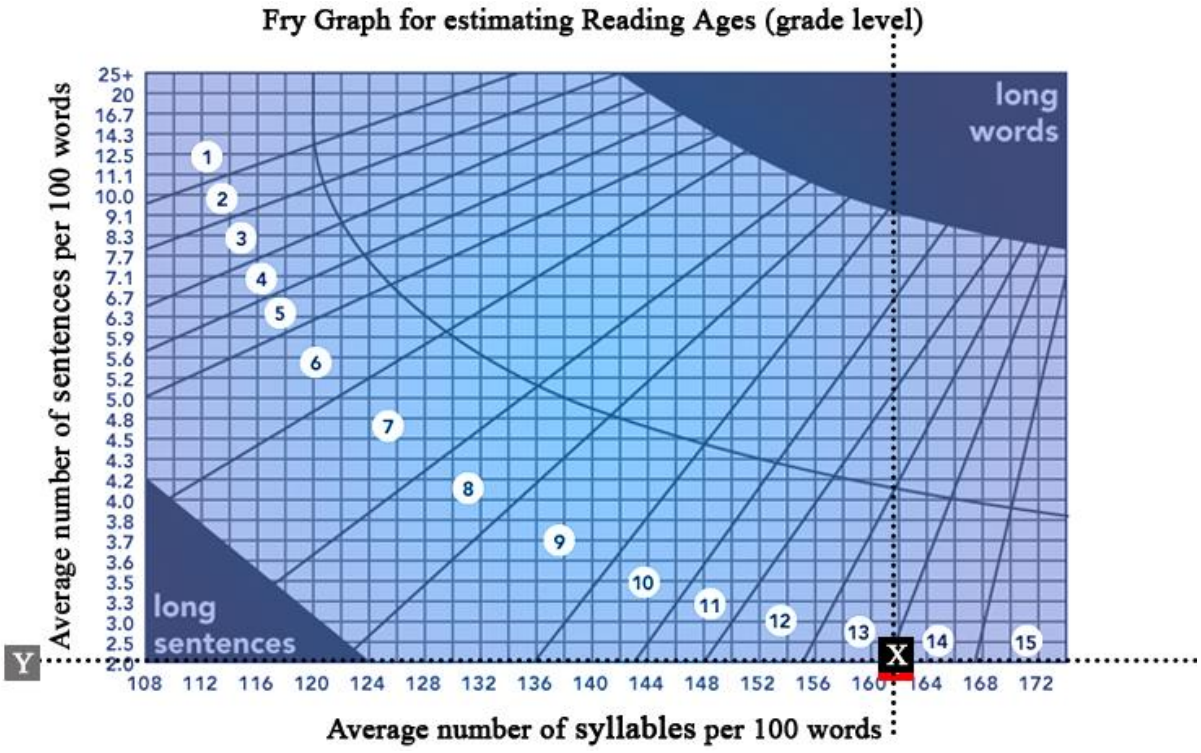
Average # of syllables per 100 words: **165**
Average # of sentences per 100 words: **4**

X = 165
Y = 4
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.2 - Possible Side-Effects continued

Sample text:
The following side-effects have been reported rarely (affecting less than 1 in 1 000 patients): • hypersensitivity (allergy) • anxiety • abnormal vision • stomach upset, dry mouth • liver or kidney problems • eczema, facial swelling, severe allergic reactions of the skin • joint pain, leg pain • influenza-like symptoms Frequency not known (cannot be estimated from the available information): • blood poisoning • anaphylactic reaction (sudden allergic reaction including signs like rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath or trouble breathing) • hives (itchy rash) • sore tendons Not all side-effects reported for MICARDIS are included in this leaflet. Should your general health worsen while taking MICARDIS, please consult your doctor, pharmacist, or other healthcare professional for advice.

FRY GRAPH



Average # of syllables per 100 words: **161**
Average # of sentences per 100 words: **1.4**


= 161


= 1.4


= Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

APPENDIX 2.6

Fry Graphs- TWYNSTA

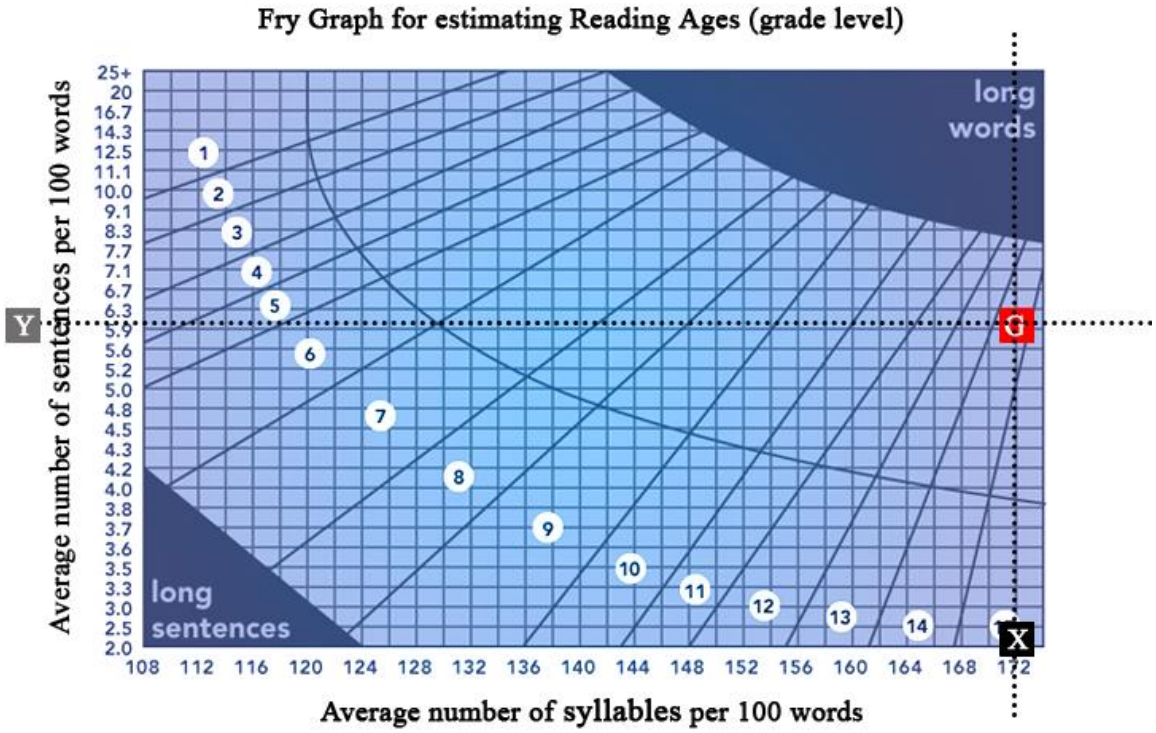
NB: The number between the two parallel lines represents the U.S. grade level.

Section 1- What Twynsta Contains

Sample text:

TWYNSTA 40/5 mg tablets: Each tablet contains 40 mg telmisartan and 5 mg amlodipine base (as besylate salt). TWYNSTA 40/10 mg tablets: Each tablet contains 40 mg telmisartan and 10 mg amlodipine base (as besylate salt). TWYNSTA 80/5 mg tablets: Each tablet contains 80 mg telmisartan and 5 mg amlodipine base (as besylate salt). TWYNSTA 80/10 mg tablets: Each tablet contains 80 mg telmisartan and 10 mg amlodipine base (as besylate salt). The other ingredients are colloidal anhydous silica, FD&C blue No. 1 aluminium lake, ferric oxide yellow, magnesium stearate, maize starch, meglumine, microcystalline cellulose, povidone K25, pregelatinised starch, sodium

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **171**
Average # of <u>sentences</u> per 100 words: **6**

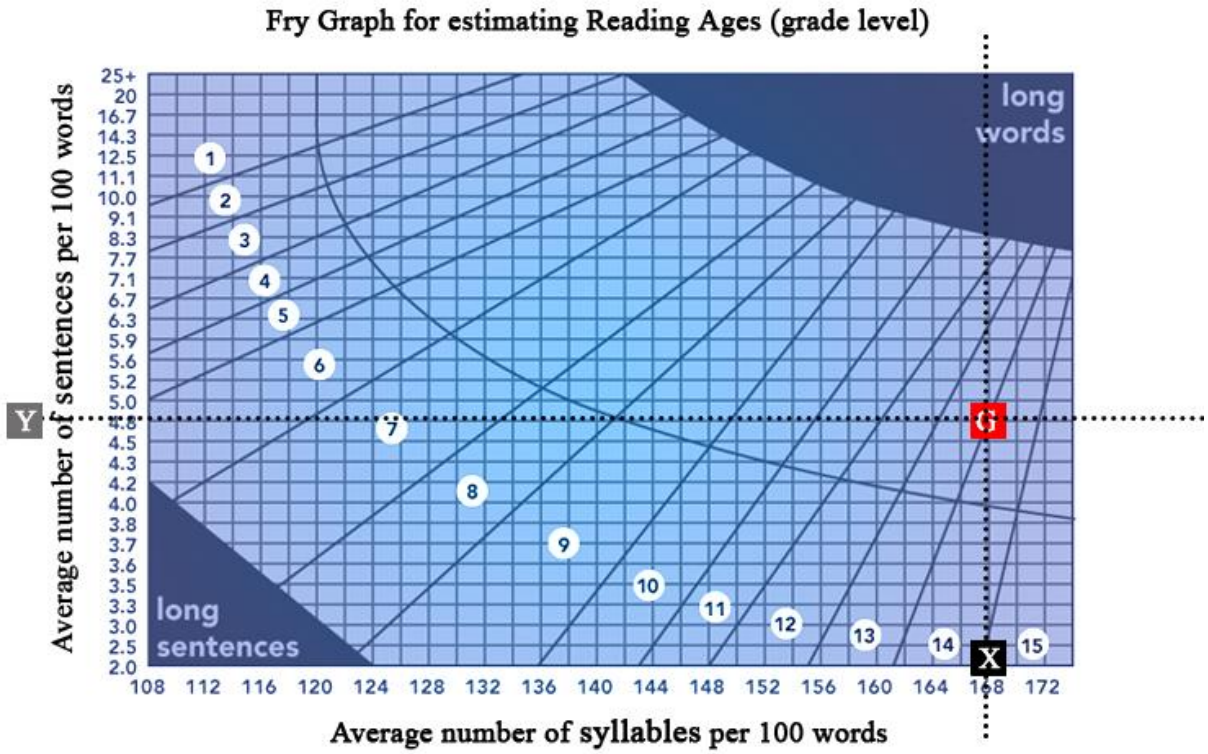
X = 171
Y = 6

G= Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 2- What Twynsta Is Used For

Sample text:
WHAT TWYNSTA IS USED FOR TWYNSTA is used to treat high blood pressure (also known as essential hypertension) in patients using the same components as individual components, or when treatment with amlodipine alone did not lower your blood pressure enough.2. WHAT TWYNSTA IS USED FOR TWYNSTA is used to treat high blood pressure (also known as essential hypertension) in patients using the same components as individual components, or when treatment with amlodipine alone did not lower your blood pressure enough.2. WHAT TWYNSTA IS USED FOR TWYNSTA is used to treat high blood pressure (also known as essential hypertension) in patients using the same components as individual components, or when treatment with amlodipine alone did not lower your blood pressure enough.

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **167**
Average # of <u>sentences</u> per 100 words: **4.9**

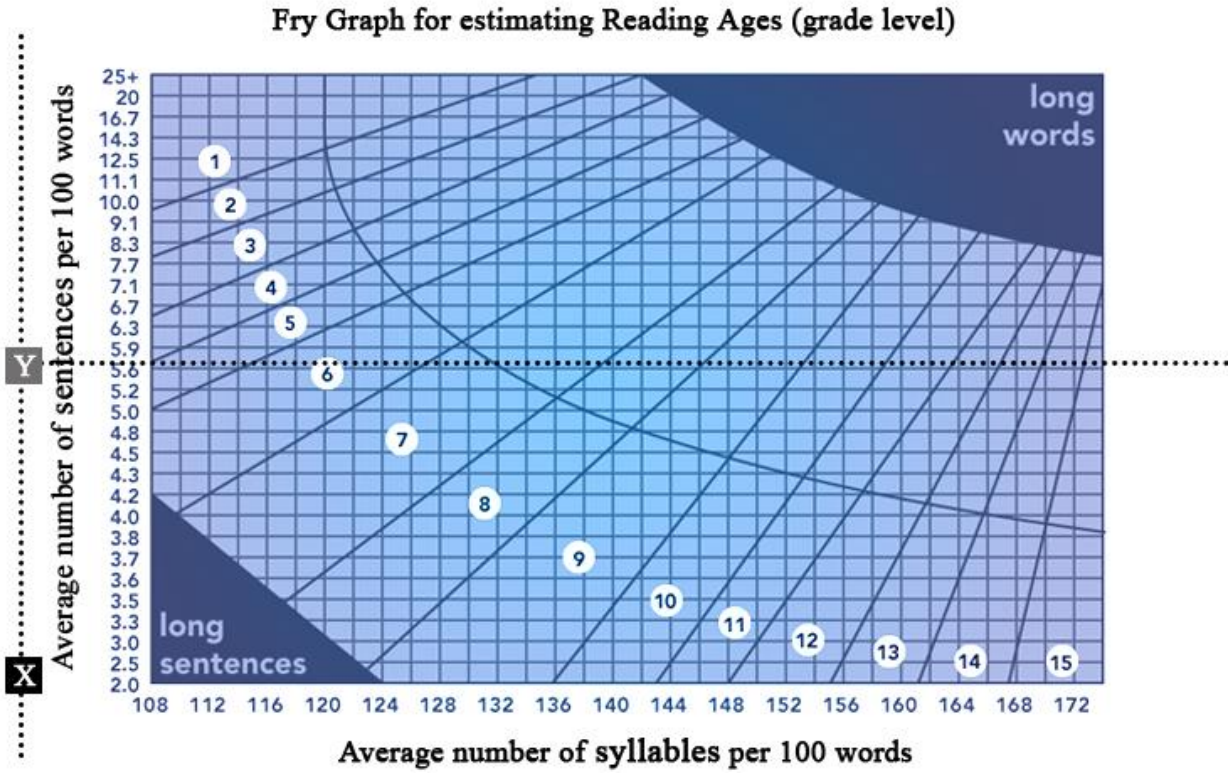
X= 167
Y= 4.9

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.1- Before You Take Twynsta

Sample text:
BEFORE YOU TAKE TWYNSTA Do not take TYWNSTA if you are pregnant, are considering becoming pregnant or are breast-feeding. A switch to a suitable alternative treatment should be carried out in advance of planned pregnancy. Do not take TWYNSTA: • If you are allergic to telmisartan, amlodipine or any of the other ingredients included in TWYNSTA tablets. • If you are allergic to other medicines of the dihydropyridine type (one type of calcium channel blocker). • Do not combine TWYNSTA with any other products containing amlodipine. • If you suffer with from a rare hereditary condition called fructose intolerance. • If you have developed swelling and giant wheals on your skin when having previously taken medicines called angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs). • If you have a narrowing of the aortic blood vessel. • If both blood vessels to the kidneys are narrowed or if you have a single kidney and the blood vessel to the kidney is narrowed.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

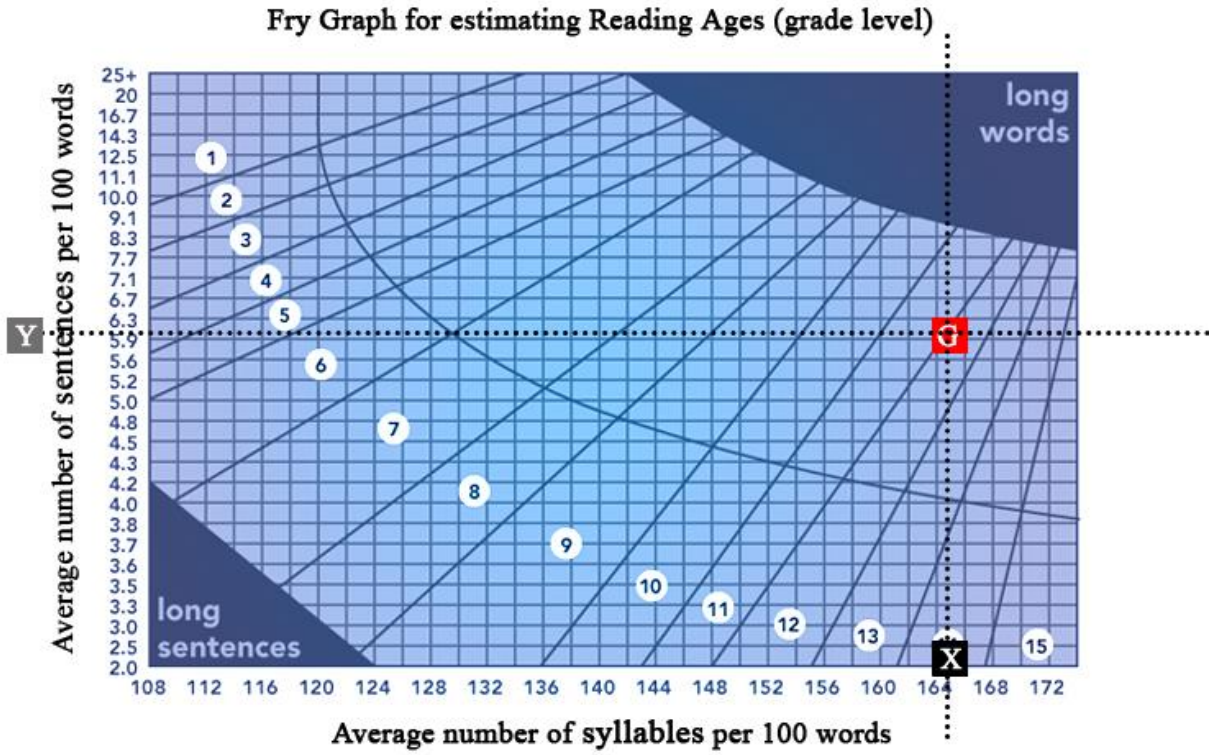
Average # of syllables per 100 words: **176**
Average # of sentences per 100 words: **5.7**

 = 176
 = 5.7
 = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.2 - Before You Take Twynsta continued

Sample text:
• If you suffer from severe liver problems. • If you suffer from biliary obstruction (a problem with the drainage of the bile from the liver and gall bladder). • If you suffer from porphyria. • If you are currently taking lithium or potassium sparing water tablets containing spironolactone, triamterene or amiloride. • If you suffer from low heart output because of a serious heart problem. • If you suffer from severe renal impairment. Take special care with TWYNSTA and tell your doctor: Please tell your doctor if you are suffering or have ever suffered from any of the following conditions or illnesses: • If you suffer from kidney disease or have had a kidney transplant. • If you suffer from liver problems. • If you have heart problems. • If you already take a medicine called an angiotensin converting enzyme inhibitor (ACE-I). • If you have been told that you have raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals). • If you have low blood pressure (hypotension), which is likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to diuretic therapy (•water tablets•), low-salt diet, diarrhoea, o vomiting. • If you have high potassium levels in your blood or use salt substitutes that contain potassium. In case of surgery or anaesthesia, you should tell your doctor that you are taking TWYNSTA. The use of TWYNSTA in children and adolescents up to the age of 18 years is not recommended.

FRY GRAPH



Average # of syllables per 100 words: **164**
Average # of sentences per 100 words: **6.1**

X = 164

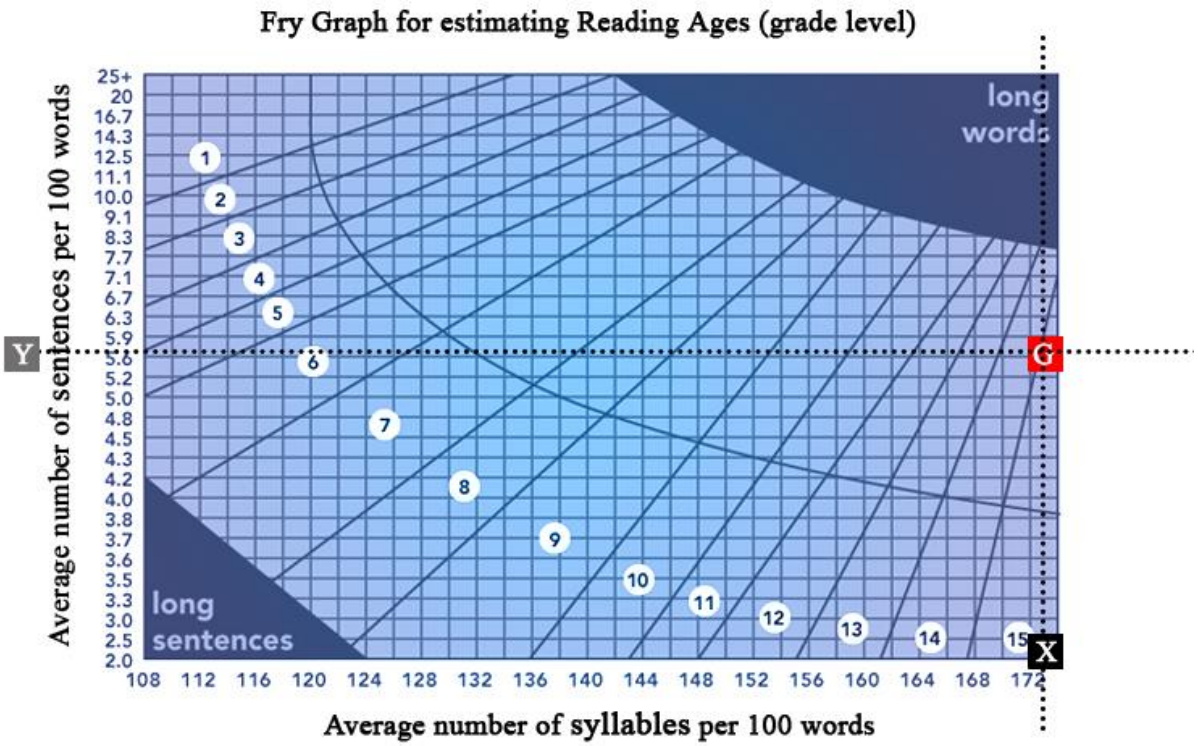
Y = 6.1

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.3- Before You Take Twynsta continued

Sample text:
Taking TWYNSTA with food and drink: You can take TWYNSTA with water or other non-alcoholic drink and with or without food. Pregnancy and breast-feeding: Do not take TWYNSTA and tell your doctor if you are pregnant, are considering becoming pregnant or are breast-feeding. A switch to a suitable alternative treatment should be carried out in advance of planned pregnancy. Driving and using machines: No information is available on the effect of TWYNSTA on the ability to drive or operate machinery. Some people may experience side-effects such as fainting, sleepiness, dizziness or a feeling of spinning (vertigo) when they are treated for high blood pressure. If you experience these side-effects, do not drive or operate machinery. Important information about some of the ingredients of TWYNSTA: TWYNSTA contains sorbitol. Sorbitol is not suitable for patient with hereditary fructose intolerance.

FRY GRAPH



Average # of <u>syllables</u> per 100 words: **172**
Average # of <u>sentences</u> per 100 words: **5.6**

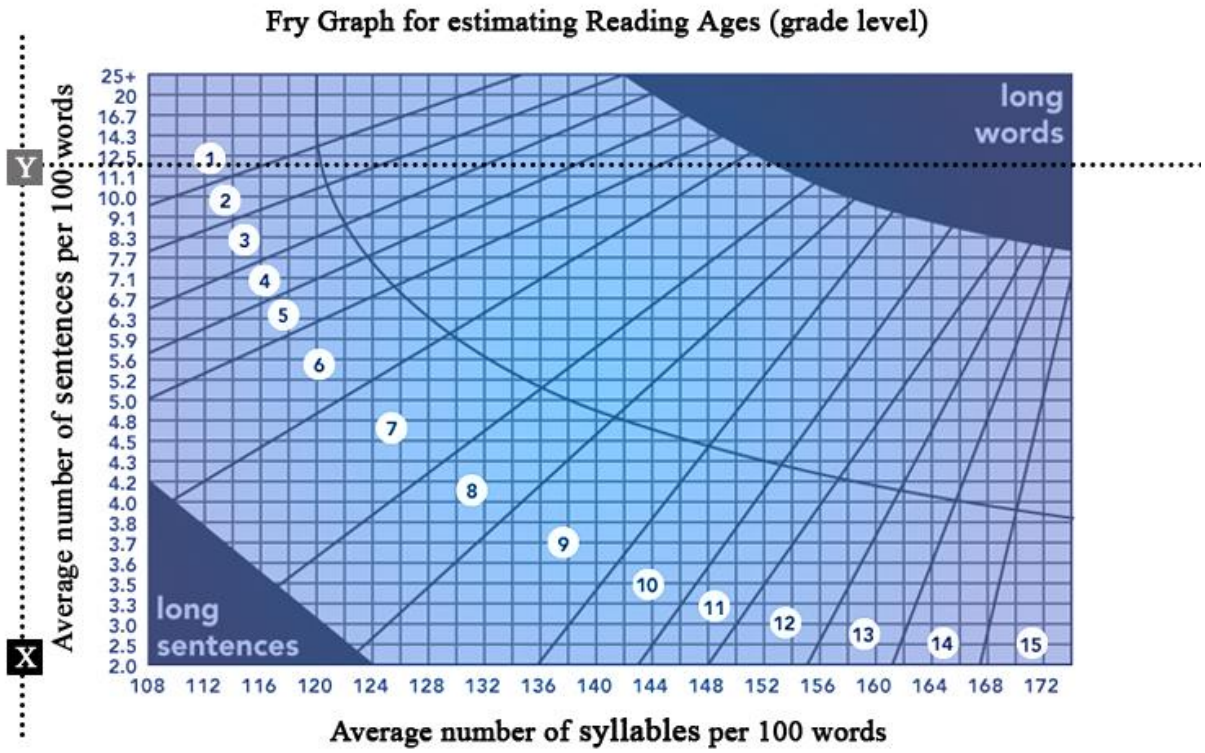
X = 172
Y = 5.6
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 3.4- Before You Take Twynsta continued

Sample text:
Taking other medicines with TWYNSTA: If you are taking other medicines on a regular basis, including complementary or traditional medicines, concomitant use of TWYNSTA may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional for advice. In some cases, you may have to stop taking one of the medicines. This applies especially to medicines listed below when taken together with TWYNSTA: Digitalis glycosides (digoxin) which is a heart medication. Lithium- containing medicines used to treat some types of depression. Anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone). Rifampicin St. John's wort Medicines used for HIV/AIDS (e.g. ritonavir) or for treatment of fungal infections (e.g. ketoconazole, itraconzaole). The effect of TWYNSTA may be reduced when you take NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen) or corticosteroids. TWYNSTA may increase the blood pressure lowering effect of other medicines used to treat high blood pressure or of

medicines with blood pressure lowering potential (e.g. antidepressants, barbiturates, narcotics) or alcohol.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of <u>syllables</u> per 100 words: **212**
Average # of <u>sentences</u> per 100 words: **12**

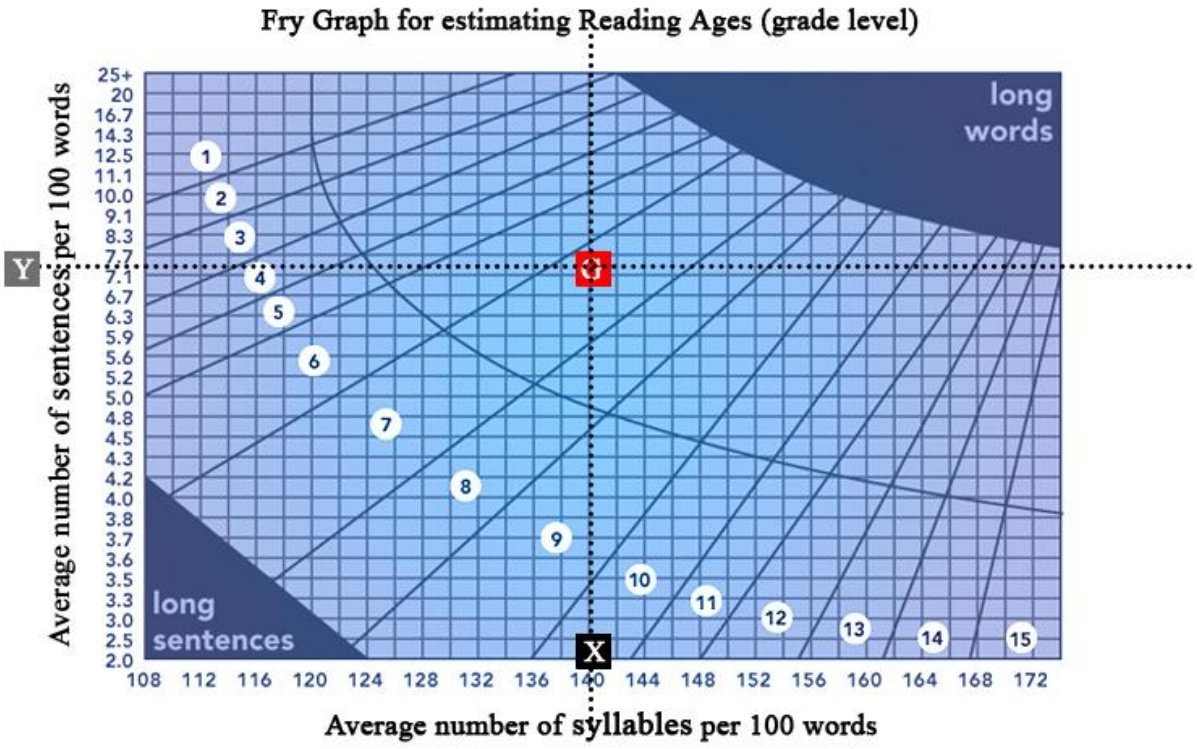
X = 212
Y = 12
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 4- How To Take Twynsta

Sample text:
HOW TO TAKE TWYNSTA Always take TWYNSTA exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual dose of

TWYNSTA is one tablet per day. Try to take the tablet at the same time each day. Remove your TWYNSTA tablets from the blister only immediately prior to intake. You can take TWYNSTA with or without food. The tablets should be swallowed with some water or other non-alcoholic drink. It is important that you take TWYNSTA every day until your doctor tells you otherwise. If you have the impression that the effect of TWYNSTA is too strong or too weak, talk to your doctor or pharmacist. If your liver is not working properly, the usual dose should not exceed TWYNSTA 40/5 mg or TWYNSTA 40/10 mg once daily. If you take more TWYNSTA than you should: In the event of overdosage or accidental intake, consult your doctor or pharmacist. If neither is available, seek help at the nearest hospital or poison control centre. If you forget to take TWYNSTA: If you forget to take a dose, do not worry. Take it as soon as you remember on the same day. If you do not take your tablet on that same day, take your normal dose on the next day. Do not take a double dose to make up for the forgotten individual doses.

FRY GRAPH



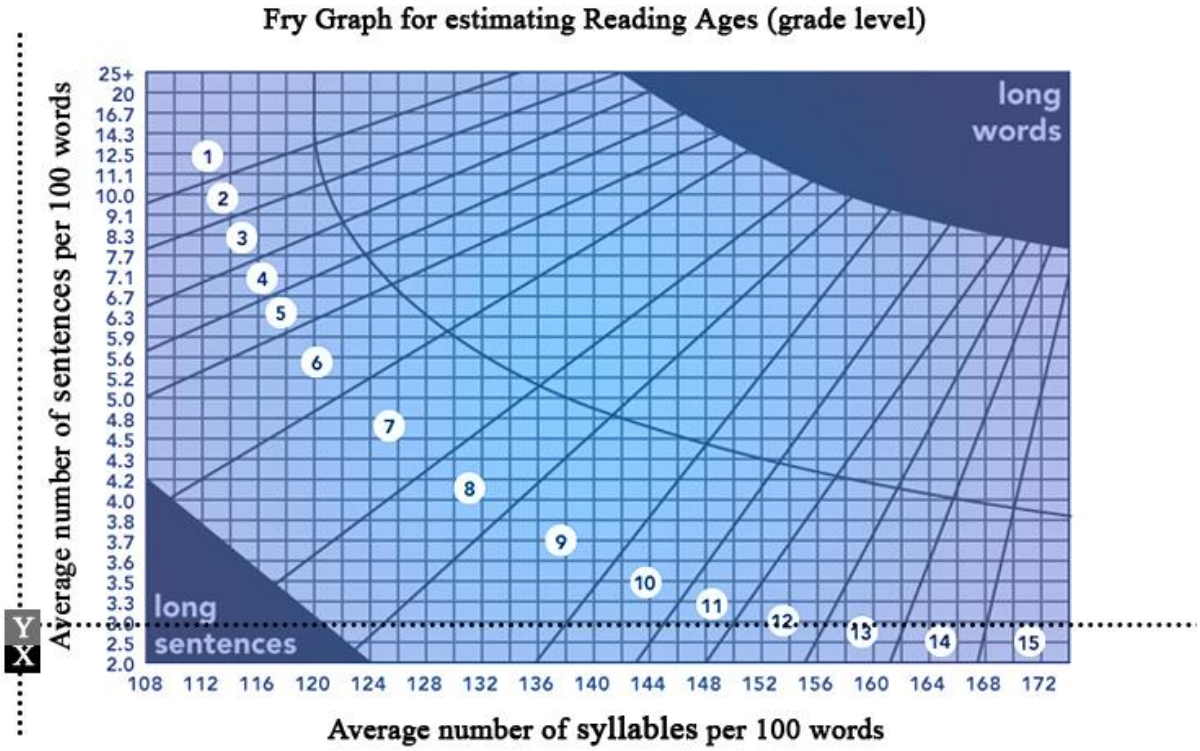
Average # of <u>syllables</u> per 100 words: **140**
Average # of <u>sentences</u> per 100 words: **7.2**

X = 140
Y = 7.2
G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.1 - Possible Side Effects

Sample text:
POSSIBLE SIDE EFFECTS TWYNSTA can have side effects. Less frequent side-effects may include: Sleepiness, migraine, headache, tingling or numbness of the hands or feet, feeling of spinning (vertigo), slow heart rate, palpitations (awareness of your heart beat), low blood pressure (hypotension), dizziness on standing up (orthostatic hypotension), flushing, cough, abdominal pain, diarrhoea, feeling sick (nausea), itching, joint pain, muscle cramps, muscle pain, inability to obtain an erection, weakness, chest pain, tiredness, swelling, increased levels of liver enzymes. Rare side-effects may include: Bladder infection, depression, feeling anxious, sleeplessness, fainting, taste abnormalities, trembling, vomiting, swollen gums, discomfort in the abdomen, dry mouth, eczema (a skin disorder), redness of skin, rash, back pain, painful limbs, urge to urinate during the night, feeling unwell, increased levels of uric acid in the blood.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of syllables per 100 words: **182**
Average # of sentences per 100 words: **3.1**

X = 182

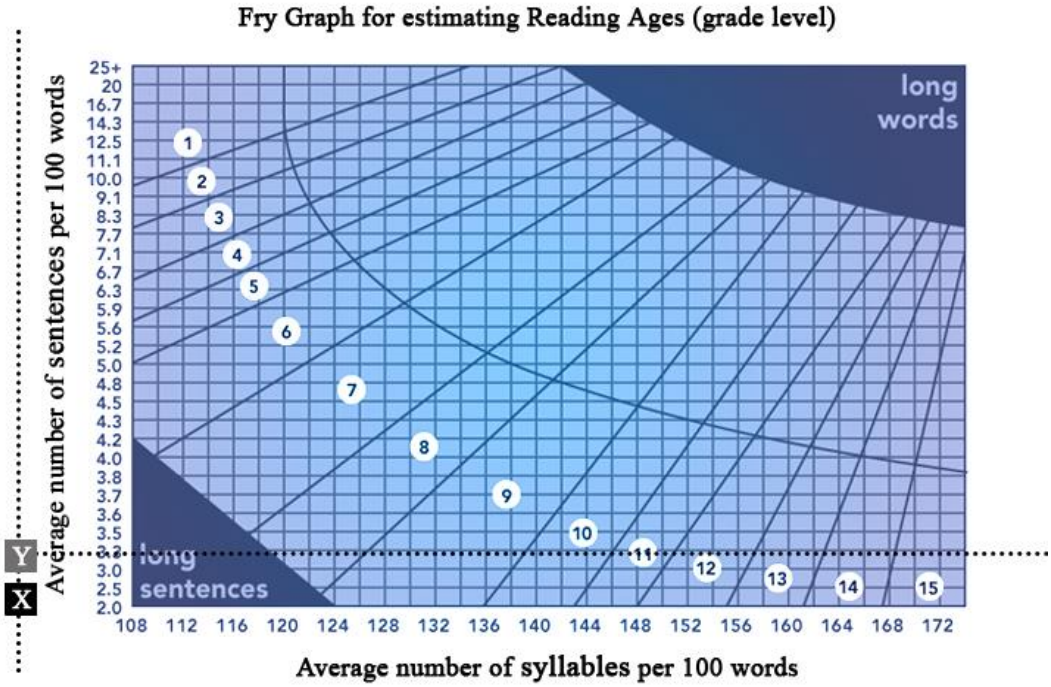
Y = 3.1

G = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.2- Possible Side Effects continued

Sample text:
Telmisartan: In patients taking telmisartan (one of the ingredients of TWYNSTA) alone the following additional side-effects have been reported, but the frequencies are not known: Sepsis (often called "blood poisoning" is a severe infection with whole body inflammatory response which can lead to death), urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), high potassium levels, impaired vision, fast heart beat, shortness of breath, bloating, stomach discomfort, abnormal liver function, rapid swelling of skin and mucosa (angioedema), increased sweating, hives (urticaria), rash, inflammation of the tendons, kidney impairment including acute kidney failure, flu-like illness, decreased haemoglobin (a blood protein), increased levels of creatinine or creatinine phosphokinase in the blood.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of <u>syllables</u> per 100 words: **196**
Average # of <u>sentences</u> per 100 words: **3.3**

X = 196

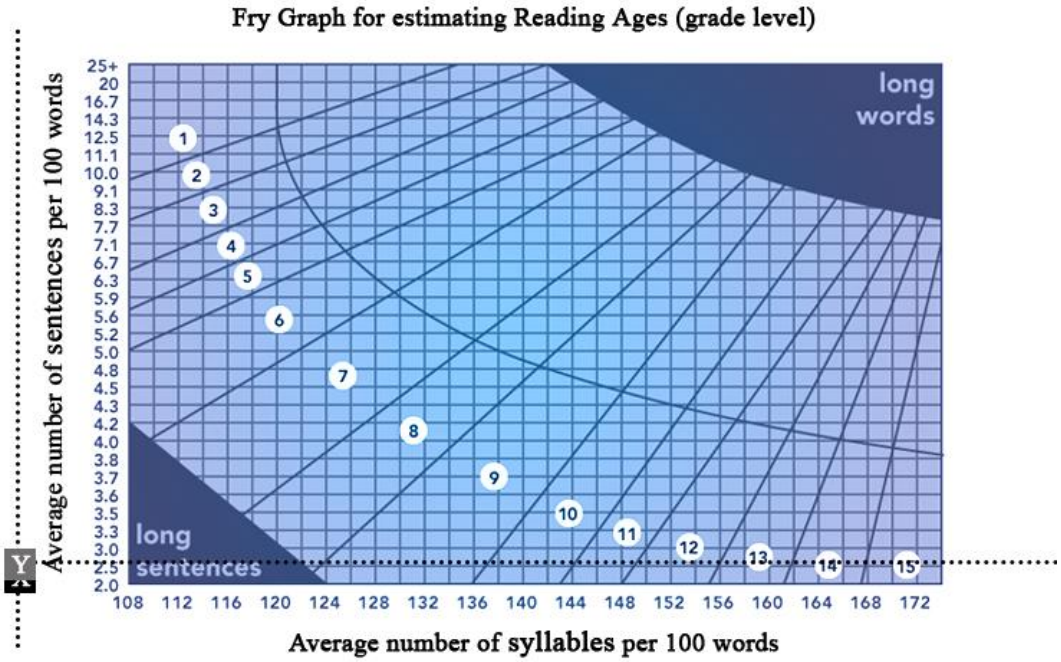
Y = 3.3

G= Grade level (the number in the white circle between the dark blue parallel lines is the grade level)

Section 5.3 - Possible Side Effects continued

Sample text:
Amlodipine In patients taking amlodipine (one of the ingredients of TWYNSTA) alone the following additional side-effects have been reported, but the frequencies are not known: Low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), excess sugar in the blood (diabetes), mood changes, impaired vision, ringing in the ears, heart attack, irregular heart beat, inflammation of the blood vessels, shortness of breath, sneezing/ runny nose, change of bowel habit, inflamed pancreas, abdominal bloating (gastritis), inflammation of the liver, yellowing of the skin (jaundice), increased levels of liver enzyme with jaundice, hair loss, unusual bruising and bleeding (red blood cell damage), skin discolouration, increased sweating, rapid swelling of skin and mucosa (angioedema), severe skin reactions, hives (urticaria), difficulty passing urine especially at night, enlarging of male breasts, pain, weight increased, weight decreased. Not all side-effects reported for TWYNSTA are included in this leaflet. Should your general health worsen while taking TWYNSTA, please consult your doctor, pharmacist or other healthcare professional for advice.

FRY GRAPH



Your text has exceeded the maximum number of syllables. The Fry Graph will not plot the X-axis on the graph.

Average # of <u>syllables</u> per 100 words: **186**
Average # of <u>sentences</u> per 100 words: **2.9**

X= 186

 = 2.9

 = Grade level (the number in the white circle between the dark blue parallel lines is the grade level)